eISSN 2958-6518
pISSN 2959-9199

Bulletin of Pharmaceutical & Medicinal Research

Volume 3 | 2024

A.A.S.E.R.
Academy for the Advancement of Science, Education & Research

BULLETIN OF
PHARMACEUTICAL & MEDICINAL RESEARCH

CONTENTS

Volume 3 | 2024 | Pages: 1 – 57

An official journal of the Academy for the Advancement of Science Education & Research (A.A.S.E.R.) published by Logixs Journals

01
Viewpoint

05
Articles

Volume Articles

Bulletin of Pharmaceutical & Medicinal Research (BPMR) is a peer-reviewed, open-access journal that provides a platform for national and international researchers to share their latest scientific findings in pharmaceutical and medicinal research. BPMR covers various interdisciplinary fields, such as pharmaceutics, pharmaceutical chemistry, basic medical sciences, pharmacology, pharmacognosy, and pharmacy practice.

Bulletin of Pharmaceutical & Medicinal Research is published by Logixs Journals on behalf of the Academy for the Advancement of Science, Education & Research (A.A.S.E.R.).

eISSN: 2958-6518

pISSN: 2959-9199

Editorial Office: 125-A, AEHS, Kheyaban-e-Jinnah Road, Lahore - 54600, Pakistan

Editorial Office: 51-A, AEHS, Kheyaban-e-Jinnah Road, Lahore - 54600, Pakistan

Guide for Authors: For submission guidelines, please go to https://logixsjournals.com/journals/5/author-guide

Editorial Policy: For editorial policies, go to https://logixsjournals.com/journals/5/editorial-policy

Print Subscription: For more information, go to https://logixsjournals.com/journals/5/pages/8

Advertising Policy: Acceptance of advertising in this journal in no way implies endorsement of the advertised product or service by Logixs Journals, A.A.S.E.R., or the journal editor(s). We reserve the right to reject any advertising it deems as inappropriate for the journal.

Indexing & Abstracting:

ISSN Network
Crossref
Google Scholar
CORE (COnnecting REpositories)

BULLETIN OF

PHARMACEUTICAL & MEDICINAL RESEARCH

Volume 3 | 2024

BOARD OF EDITORS

Bulletin of
Pharmaceutical & Medicinal Research

Viewpoint

Artificial intelligence and the pharmaceutical industry: transforming research, development, and manufacturing

Nazneen Fatima

Faculty of Pharmacy, University of Sindh, Jamshoro, Pakistan

Correspondence: fatimanazneen80@gmail.com

Citation: Fatima N. Artificial intelligence and the pharmaceutical industry: transforming research, development, and manufacturing. Bull Pharm Med Res. 2024;3:1-4.

Received: 09 October 2024
Revised: 22 November 2024
Accepted: 27 November 2024
Published: 31 December 2024

Publisher's Note: Logixs Journals remains neutral concerning jurisdictional claims in its published subject matter, including maps and institutional affiliations.

Extract

Artificial intelligence (AI) with the amalgamation of information technology is an important driver of transformation in every field of life, including the pharmaceutical industry. From the early stages of drug discovery, extraction, and formulation, followed by improvement and precision in manufacturing, AI has helped the pharmaceutical industry work more effectively and efficiently in the production of the highest-quality products. Machine learning (ML) algorithms can easily analyze large datasets in no time to identify potential pharmaceutically effective drugs, characteristics of experiments, parameters of testing, optimize clinical trial designs, and monitor pharmaceutical production processes in real time. These operations significantly reduce drug development time, costs, and effort; ease complexities; and improve safety and effectiveness, ultimately providing a competitive edge to many pharmaceutical companies across the globe. However, the incorporation of AI into pharmaceutical systems also presents significant challenges; for example, many pharmaceutical companies face issues with inconsistent or incomplete data, a lack of domain-specific technical human resources, and uncertain, debatable ethical concerns, particularly related to privacy, algorithmic fairness, and transparency in decision-making. The benefits and advantages of using AI may remain limited until pharmaceutical companies invest in high-quality data infrastructure, interdisciplinary training of professionals, and clear regulatory frameworks for procedures. This calls for vital collaboration and joint ventures among pharmaceutical companies, manufacturing units, research institutions, technology providers, informational technology houses, drug regulatory bodies, and academia to transform the pharmaceutical landscape by making drug development faster, cheaper, safer and more responsive to global health needs.

Keywords

Artificial intelligence; Pharmaceutical industry; Manufacturing precision; Industry 4.0; Healthcare technology; Drug discovery

Artificial intelligence (AI) has proven to be important for every walk of life and has become increasingly popular across various sectors worldwide because of its benefits and efficiency in reducing human effort and time [1]. AI has five major branches, including machine learning (ML) (learning for the data and improving over time without being programmed), deep learning (using artificial neural networks and mimicking the human brain), natural language processing (understanding, interpreting and generating human language), computer vision (understanding visual information) and robotics (performing autonomous tasks with the integration of physical mechanics) [2,3].

The pharmaceutical industry, which is a major component of the healthcare system, plays a vital role in disease prevention, prophylaxis, treatment, and research. The use of AI in the pharmaceutical sector has not only reduced human effort and human errors but also saved time, energy, and cost and has introduced a variety of horizons in drug devel-

opment, clinical trials, and postmarking surveillance of pharmaceuticals [4]. Large language-based systems of AI equip pharmaceuticals with faster hypothesis generation and evidence-based decision making with the help of data in all stages of a pharmaceutical services chain [5]. It is estimated that the use of AI in pharmaceutical sciences for manufacturing, research and development will increase the pharmaceutical market from USD 0.64 billion in 2024 to 34.8 billion by 2040 across the globe [6].

AI has now simplified the drug development process, an activity that costs the industry approximately 2.8 billion USD and 10 years of time, with 90% of therapeutic molecules failing to successfully complete phase II trials [7,8]. AI helps in repurposing known drug molecules that can directly take part in phase II trials and costs the industry approximately 2.6 billion USD for drug development from scratch [9]. The application of AI for improving clinical trial design, predicting patient responses, and managing regulatory documentation potentially reduces the development time by 25–40% and the annual cost of the pharmaceutical industry by 100 billion USD [10].

The integration of technologies such as "Industry 4.0" and "Quality by Design" (QbD) has reshaped pharmaceutical manufacturing by streamlining production through automation, standardization, quality control and risk management. Many pharmaceutical manufacturing units have incorporated QbD to gain a comprehensive understanding of product production processes [11,12]. A computer-aided program helps to effectively resolve formulation design-related problems and improves the stability of the finished products [13]. AI algorithms not only help to enhance the quality of service but also optimize production processes via effective quality risk management [14,15]. Recent studies highlight how AI-driven process control, predictive maintenance, and real-time monitoring are transforming pharmaceutical manufacturing compliance under good manufacturing practices (GMPs), while regulators are developing new frameworks to ensure the safe and transparent use of AI in production [16,17].

Despite the benefits of AI integration in the pharmaceutical sector, the availability of reliable datasets, lack of trained professionals in information technology, financial constraints, fear of job displacement and the "black box" aspect of AI pose a challenge for the pharmaceutical industry to AI in the routine operations of the industry [18]. Furthermore, no AI-developed drug has yet fully obtained regulatory approval from authentic international regulatory agencies [19,20]. To gain the complete benefits of AI in pharmaceutical manufacturing and research, overcoming these major barriers with intersectoral coordination and policy development is important [21,22]. Ethical issues such as issues of data privacy, algorithmic bias, and concerns of job replacement need to be addressed to ensure the worthwhile and appropriate use of AI in pharmacies [23].

In summary, AI is considered an incentive for pharmaceutical innovation, as it responds to major challenges such as drug development costs, time, safety and manufacturing accuracy. However, successful integration involves overcoming quality problems in data, a lack of trained experts, and ethical issues. The growing evidence base and rapid technological advances in the contemporary world strongly justify AI's transformative role in achieving faster, safer, and more cost-effective pharmaceutical development, supporting the argument that AI integration is not only beneficial but also essential for the pharmaceutical industry's future [24]. By strategically integrating AI into pharmaceutical manufacturing and research, the industry can achieve significant advancements, enhancing global healthcare.

Author contributions: The editorial was written and revised by the author herself.

Funding: This research received no specific grant from the public, commercial, or not-for-profit funding agencies.

Ethics statement: Not Applicable.

Consent to participate: Not Applicable.

Data availability: Not applicable.

Acknowledgments: None.

Conflicts of interest: The author declares no conflicts of interest.

References

[1] Alabdulatif A. The global impact of artificial intelligence. In: Mabrouki J, Mourade A, editors. Technical and Technological Solutions Towards a Sustainable Society and Circular Economy. 1st ed. Cham: Springer Nature; 2024. p. 263-77.
[2] Swanson K, Wu E, Zhang A, Alizadeh AA, Zou J. From patterns to patients: advances in clinical machine learning for cancer diagnosis, prognosis, and treatment. Cell. 2023;186(8):1772-91. https://doi.org/10.1016/j.cell.2023.01.035
[3] Sahu A, Mishra J, Kushwaha N. Artificial intelligence (AI) in drugs and pharmaceuticals. Comb Chem High Throughput Screen. 2022;25(11):1818-37. https://doi.org/10.2174/1386207325666211207153943
[4] Serrano DR, Luciano FC, Anaya BJ, Ongoren B, Kara A, Molina G, et al. Artificial intelligence (AI) applications in drug discovery and drug delivery: revolutionizing personalized medicine. Pharmaceutics. 2024;16(10):1328. https://doi.org/10.3390/pharmaceutics16101328
[5] Zhang P, Kamel Boulos MN. Generative AI in medicine and healthcare: promises, opportunities and challenges. Future Internet. 2023;15(9):286. https://doi.org/10.3390/fi15090286
[6] Roots Analysis. AI in drug manufacturing market. 2024 [cited 15 July 2024]. Available from: https://www.rootsanalysis.com/reports/ai-in-drug-manufacturing-market.html.
[7] Alvarez-Machancoses O, Fernandez-Martinez JL. Using artificial intelligence methods to speed up drug discovery. Expert Opin Drug Discov. 2019;14(8):769-77. https://doi.org/10.1080/17460441.2019.1621284
[8] Fleming N. How artificial intelligence is changing drug discovery. Nature. 2018;557:S55-7. https://doi.org/10.1038/d41586-018-05267-x
[9] Sarkar C, Das B, Rawat VS, Wahlang JB, Nongpiur A, Tiewsoh I, et al. Artificial intelligence and machine learning technology driven modern drug discovery and development. Int J Mol Sci. 2023;24(3):2026. https://doi.org/10.3390/ijms24032026
[10] MedPath. Generative AI poised to transform clinical trial efficiency with 40% faster regulatory submissions. 2024 [cited 15 July 2024]. Available from: https://trial.medpath.com/news/72360b3d077886ab/generative-ai-poised-to-transform-clinical-trial-efficiency-with-40-faster-regulatory-submissions.
[11] Paul D, Sanap G, Shenoy S, Kalyane D, Kalia K, Tekade RK. Artificial intelligence in drug discovery and development. Drug Discov Today. 2021;26(1):80-93. https://doi.org/10.1016/j.drudis.2020.10.010
[12] Miller JA, Fredrickson ME, Greene JM, Jay M, Oyewumi MO. Reimagining drug manufacturing paradigm in today's pharmacy landscape. J Am Pharm Assoc. 2022;62(6):1761-4. https://doi.org/10.1016/j.japh.2022.08.024
[13] Kontogeorgis GM, Jhamb S, Liang X, Dam-Johansen K. Computer-aided design of formulated products. Curr Opin Colloid Interface Sci. 2022;57:101536. https://doi.org/10.1016/j.cocis.2021.101536
[14] Ejjami R, Boussalham K. Industry 5.0 in manufacturing: enhancing resilience and responsibility through AI-driven predictive maintenance, quality control, and supply chain optimization. Int J Multidiscip Res. 2024;6(4):240425733. https://doi.org/10.36948/ijfmr.2024.v06i04.25733
[15] Kot S, Hussain HI, Bilan S, Haseeb M, Mihardjo LWW. The role of artificial intelligence recruitment and quality to explain the phenomenon of employer reputation. J Bus Econ Manag. 2021;22(4):867-83. https://doi.org/10.3846/jbem.2021.14606
[16] Saha GC, Eni LN, Saha H, Parida PK, Rathinavelu R, Jain SK, et al. Artificial intelligence in pharmaceutical manufacturing: enhancing quality control and decision making. Riv Ital Filos Anal Jr. 2023;14(2):2023.
[17] Subramanian S. Leveraging IoT data streams for AI-based quality control in smart manufacturing systems in process industry. J AI-Assist Sci Discov. 2023;3(1):784-820.
[18] Lamberti MJ, Wilkinson M, Donzanti BA, Wohlhieter GE, Parikh S, Wilkins RG, et al. A study on the application and use of artificial intelligence to support drug development. Clin Ther. 2019;41(8):1414-26. https://doi.org/10.1016/j.clinthera.2019.05.018
[19] The Lancet. AI in medicine: creating a safe and equitable future. Lancet. 2023;402(10401):503. https://doi.org/10.1016/S0140-6736(23)01668-9
[20] Druedahl LC, Price WN, Minssen T, Sarpatwari A. Use of artificial intelligence in drug development. JAMA Netw Open. 2024;7(5):e2414139. https://doi.org/10.1001/jamanetworkopen.2024.14139
[21] Morin O, Vallières M, Braunstein S, Ginart JB, Upadhaya T, Woodruff HC, et al. An artificial intelligence framework integrating longitudinal electronic health records with real-world data enables continuous pan-cancer prognostication. Nat Cancer. 2021;2:709–22. https://doi.org/10.1038/s43018-021-00236-2
[22] Jacoba CMP, Celi LA, Silva PS. Biomarkers for progression in diabetic retinopathy: expanding personalized medicine through integration of AI with electronic health records. Semin Ophthalmol. 2021;36(4):250–7. https://doi.org/10.1080/08820538.2021.1893351

[23] Reddy S, Allan S, Coghlan S, Cooper P. A governance model for the application of AI in health care. J Am Med Inform Assoc. 2020;27(3):491–7. https://doi.org/10.1093/jamia/ocz192
[24] Vora LK, Gholap AD, Jetha K, Thakur RRS, Solanki HK, Chavda VP. Artificial intelligence in pharmaceutical technology and drug delivery design. Pharmaceutics. 2023;15(7):1916. https://doi.org/10.3390/pharmaceutics15071916

Bulletin of
Pharmaceutical & Medicinal Research

Original Article

Hepatoprotective and antidiabetic effects of Cichorium intybus seed extract in alloxan-induced diabetic mice: a histopathological evaluation

Muhammad Hamza [a], Hamza Asghar [b,*], Javeria Saghir [c], Aiman Riaz [b], Zarish Suhail [b]

[a] Department of Zoology, University of Education, Pakistan
[b] University of Health Sciences, Lahore, Pakistan
[c] Northeast Normal University, Changchun, Jilin, China

* Correspondence: hamzaasghar233@gmail.com

Citation: Hamza M, Asghar H, Saghir J, Riaz A, Suhail Z. Hepatoprotective and antidiabetic effects of Cichorium intybus seed extract in alloxan-induced diabetic mice: a histopathological evaluation. Bull Pharm Med Res. 2024;3:5-14.

Received: 01 July 2024
Revised: 27 September 2024
Accepted: 16 October 2024
Published: 31 December 2024

Publisher's Note: Logixs Journals remains neutral concerning jurisdictional claims in its published subject matter, including maps and institutional affiliations.

Abstract

Diabetes mellitus (DM) is a chronic metabolic disorder associated with hepatic dysfunction caused by persistent oxidative stress and hyperglycemia. The establishment of safe plant-based therapies to manage diabetes-related hepatic injury has been an important research area. This experimental study determined the hepatoprotective effect of Cichorium intybus (Kasni) seed extract on alloxan-induced diabetes in mice via histopathological evaluation. Thirty male albino mice were selected and randomly divided into three groups (n = 10 each): the nondiabetic control group, the diabetic untreated group, and the diabetic Kasni-treated group. Type 2 diabetes was induced by the intraperitoneal administration of alloxan monohydrate (150 mg/kg). Aqueous extracts of Kasni seeds (400 mg/kg) were orally administered once a day for 28 days to the mice in the treatment group, and gross liver morphology and histological features were studied for changes via hematoxylin and eosin (H&E) staining. The results of the present study revealed that untreated diabetic mice presented elevated blood glucose levels, enlarged pale livers, and histological features indicating hepatic injury, including hepatocellular vacuolation, sinusoidal congestion, and early pericentral fibrosis. Diabetic mice treated with Kasni presented near-normal hepatic histological features; furthermore, the structure of the central vein was restored, orderly hepatocyte plates formed, and no inflammation, steatosis or fibrosis was observed. The gross morphological features revealed that the liver color and texture were similar to those of the control group. The study concluded that Cichorium intybus has a hepatoprotective effect against diabetes-related liver damage because of the antioxidant and anti-inflammatory properties of the active ingredients in the plant.

Keywords

Cichorium intybus; Kasni seeds; Hepatoprotective effects; Histological analysis; Diabetes-induced mice; Alloxan; Liver health

1. Introduction

Type 2 diabetes mellitus (T2DM) is an insulin-resistant metabolic disorder that is characterized by metabolic dysregulation, progressive β-cell dysfunction and insulin resistance; therefore, the role of the liver is important in both the pathogenesis and complications of diabetes [1]. The prevalence of diabetes across the globe is increasing, and it is estimated that 589 million people from 20-79 years of age are suffering from diabetes; furthermore, the global prevalence is estimated to exceed 700 million individuals by the year 2045 [2,3]. Despite advancements in pharmaceutical drug development and manufacturing technologies, conventional pharmacological agents, including metformin, sul-

fonylureas, and thiazolidinediones, have been proven to be ineffective in organ protection, mitigating adverse effects, and increasing patient compliance [4,5].

Chronic hyperglycemia and insulin resistance generate oxidative stress, lipotoxicity, and inflammation in liver cells, which leads to structural and functional liver damage [6,7]. Therefore, natural compounds with multitarget antioxidant, anti-inflammatory, and hepatoprotective activities have attracted scientific interest as potential adjuncts to standard pharmacological therapy [8,9]. Medicinal plants remain a key source of novel bioactive compounds, and numerous phytochemicals have been shown to improve insulin sensitivity and protect hepatic architecture in preclinical models of diabetes [10].

Among these, Cichorium intybus L. (chicory; commonly known as Kasni) is a medicinal herb with a long ethnopharmacological history in Unani and Ayurvedic medicine [11,12]. Its phytochemical profile includes inulin-type fructans, chicoric acid, chlorogenic acid, sesquiterpene lactones, flavonoids, and phenolic acids that collectively contribute to antioxidant, hypoglycemic, and hepatoprotective actions [13,14]. Recent mechanistic evidence indicates that these compounds modulate AMPK and PPARα signaling, suppress NF-κB activation, and inhibit NLRP3 inflammasome assembly, thereby mitigating hepatic oxidative injury and inflammatory cascades in diabetes and nonalcoholic fatty liver disease (NAFLD) [15,16,17].

Over the past five years, experimental and clinical studies have strengthened the scientific basis for the metabolic and hepatic benefits of chicory. Animal studies have shown that C. intybus seed and leaf extracts significantly reduce fasting glucose, serum triglyceride, and liver enzyme levels while restoring antioxidant enzyme activity and normal hepatic histology in alloxan- or streptozotocin-induced diabetic rodents [18,19,20]. Parallel clinical studies reported modest improvements in glycemic control, liver function, and inflammatory markers in patients receiving chicory supplementation [21,22]. In addition, chicory polysaccharides have been shown to reduce hepatic steatosis via AMPK activation and the downregulation of lipogenic genes [23].

Although these results are promising, there are few reports on the hepatoprotective efficacy of C. intybus seed extract in diabetic models with histopathological validation. This study investigated the hepatoprotective and antidiabetic activities of Cichorium intybus seed extract in alloxan-induced diabetic mice, with a focus on the biochemical and histopathological features of hepatic recovery.

2. Methodology

2.1. Study design and ethical approval

This controlled experimental study was designed to assess the hepatoprotective and antidiabetic effects of the seed extract of Kasni in alloxan-induced diabetic mice. The experimental work was conducted at the Department of Zoology, University of Education, Lahore, after approval was obtained from the Institutional Ethical Review Board of the University of Education, UE/IRB/2023/CHEM-011. The study is presented according to the ARRIVE 2.0 guidelines on the reporting of animal experiments to ensure reproducibility and transparency of the research [24].

2.2. Sample size determination

The study included a total of 30 mice, with 10 animals in each of the three groups. A formal a priori sample size calculation was not conducted at the time of study planning. The number of animals selected was based on practical feasibility, adherence to ethical principles for minimizing animal use, and reference to previously published alloxan-induced diabetic mouse models that commonly used approximately 10 animals per group

for histopathological and organ-level evaluation [24,25]. In line with the ARRIVE 2.0 guidelines, the study provides transparent reporting on how the sample size was determined. While adequate for preliminary assessment, this sample size may limit the statistical power of the study.

2.3. Experimental animals and housing

Thirty male albino mice (*Mus musculus*), 5–6 weeks of age and approximately 25 g, were procured from the University of Veterinary and Animal Sciences (UVAS), Lahore. Before experimentation, the mice were allowed to acclimatize for two weeks under standard laboratory conditions of temperature, humidity, and light. The animals were housed in steel cages with softwood bedding maintained at 29 ± 2 °C, 40–60% relative humidity, and a 12-h light/dark cycle, with free access to the standard pellet diet and water ad libitum. A maximum of five mice were placed in each cage, and the bedding was renewed twice a week. Nesting tissue and paper tubes were also used to reduce stress.

2.4. Induction of experimental diabetes

Type 2 diabetes was induced by intraperitoneal injection of freshly prepared alloxan monohydrate (Sigma–Aldrich, USA) at a dose of 150 mg/kg body weight dissolved in normal saline after an overnight fast. The alloxan solution was prepared just before injection and kept on ice to minimize oxidative degradation. [26,27] To avoid transient hypoglycemia, the animals were given 5% glucose solution for 24 hours post-injection. Blood glucose was measured through the tail vein via a glucometer (Accu-Chek Active, Roche Diagnostics, Germany) on the 1st, 3rd, and 7th days after injection. Animals with blood glucose levels greater than 250 mg/dL on day 7 were considered diabetic and were selected for further experiments [28,29,30].

2.5. Preparation and administration of Cichorium intybus seed extract

Seeds of kasni were obtained from a certified local herbal supplier in Lahore and authenticated by the Department of Botany, University of Education. Seeds were washed with distilled water, shade-dried at room temperature, and pulverized via an electric grinder. Five grams of seed powder was soaked overnight in 100 mL of distilled water and then heated at 70–80 °C for 15 minutes. After cooling, the mixture was filtered through Whatman No. 42 filter paper, and the filtrate was stored at 4 °C until use. A yield of 12% w/w was acquired after extraction, and the extracts were given seven days of post preparation to ensure stability.

2.6. Experimental grouping and treatment

Diabetes was induced in Groups B and C via the intraperitoneal injection of alloxan, whereas Group A served as the nondiabetic control. Blood glucose levels were checked on days 1, 3, and 7 after induction, and mice with glucose > 250 mg/dL on day 7 were considered diabetic. From day 7 onward, Group C received aqueous Kasni seed extract orally at a dose of 400 mg/kg once daily for 28 days through a micropipette, whereas Group B received a corresponding volume of normal saline. Group A received no treatment. Body weight and blood glucose levels were recorded weekly throughout the study period [31,32].

2.7. Sacrifice and tissue collection

At the end of the 28-day treatment period, all the animals were euthanized humanely via CO_2 inhalation followed by cervical dislocation, according to the American Veterinary

Medical Association (AVMA) Guidelines for Euthanasia of Animals [33]. The abdominal cavity was opened via a midline incision, and the liver was excised, rinsed gently with normal saline to remove blood, and immediately fixed in 10% neutral buffered formalin (NBF) at a tissue-to-fixative ratio of 1:10 for 48 hours. To minimize batch variability, all samples were fixed and processed within a 48-hour period.

2.8. Histopathological processing and microscopic evaluation

After fixation, the liver tissues were dehydrated through graded ethanol (70%, 80%, 90%, 95%, and 100%), cleared in xylene, and embedded in paraffin wax. The paraffin blocks were sectioned at a thickness of 4 μm via a rotary microtome (Leica RM2125 RTS, Germany). The sections were floated in a 40 °C water bath, mounted on clean slides, and dried overnight. Hematoxylin and eosin (H&E) staining was performed according to standard histological protocols [34].

For each animal, three nonconsecutive sections from three different levels of the liver block (spaced 75–100 μm apart) were prepared and examined to capture representative hepatic morphology. The slides were observed under a light microscope (Olympus BX43, Japan) at magnifications of 10×, 40×, and 100×. Photomicrographs were taken via a digital camera (Olympus DP25) attached to the microscope. All histopathological evaluations were conducted independently by three experienced histopathologists blinded to group allocation, and discrepancies were resolved by joint review. Liver sections were assessed for hepatocellular degeneration, necrosis, sinusoidal dilation, inflammation, and steatosis. Histological alterations were graded semiquantitatively according to a modified scoring system based on Kleiner et al. [35].

2.9. Histopathological analysis

Thirty mice were divided equally into three groups (n = 10 per group). The selected group size was informed by previously published alloxan-induced diabetic mouse models that commonly used approximately 10 animals per group for organ-level and histopathological evaluation [24,25]. The present sample size aligns with these precedents and reflects ethical considerations to avoid unnecessary animal use. All histological data were analyzed via GraphPad Prism version 10.0 (GraphPad Software, USA).

3. Results

3.1. Gross observations

At dissection, the livers of nondiabetic mice appeared normal, smooth, and uniformly reddish-brown with sharp margins and no visible surface nodules or congestion, indicating normal hepatic morphology. Livers from untreated diabetic mice were paler in color and presented a slightly greasy appearance, suggesting fatty changes in the liver; furthermore, mild lobular congestion was observed in some of the diabetic mice. Livers of Kasni-treated diabetic mice showed partial restoration of normal color and consistency of the liver, with no gross nodules and minimal dullness, highlighting improvement in morphological features compared with those of the untreated diabetic group.

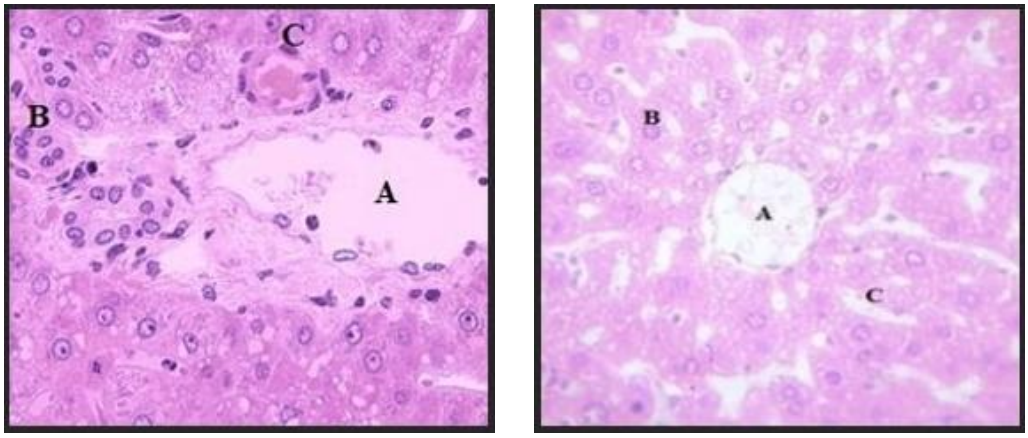
3.2. Blood glucose trends

Following alloxan administration, random blood glucose levels increased in untreated diabetic mice and Kasni-treated mice by the third day and stabilized above 250 mg/dL by day seven, confirming successful diabetes induction in these mice. Nondiabetic mice maintained normoglycemia throughout the experiment. During the 28-day treatment phase, the untreated diabetic mouse group maintained continually increased

blood glucose values (typically > 300 mg/dL), whereas the Kasni-treated mouse group revealed a progressive decline in blood glucose levels, reaching near-normal levels (~160–180 mg/dL) at the time of sacrifice.

3.3. Nondiabetic control

Liver sections from nondiabetic mice presented normal lobular features; hepatocytes were polygonal in shape with centrally placed nuclei and were arranged in a one-cell-thick line radiating from a clearly defined central vein (Figure 1). The sinusoids were narrow and regularly distributed, and the Kupffer cells were normal in number and morphology. The portal triad, consisting of the portal vein, hepatic artery, and bile duct, appeared intact without inflammation or fibrosis.

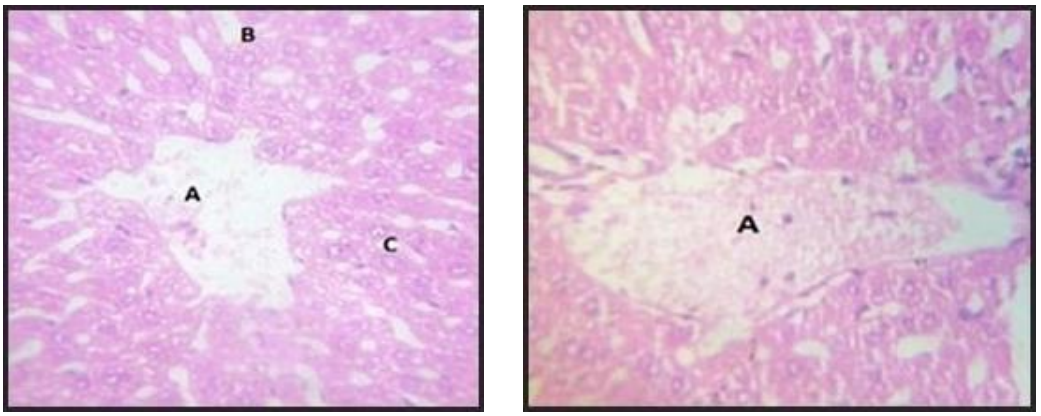


(**a**) (**b**)

Figure 1. Histology of the control group. (**a**) Portal triad showing the artery (A), bile duct (B), and portal vein (C). (**b**) Central vein (A) with radially arranged hepatocyte cords (B) and normal sinusoids (C). H&E × 400.

3.4. Diabetes untreated

In the diabetic untreated group, hepatic lobular organization was disrupted (Figure 2). The hepatocytes displayed cytoplasmic vacuolation and fatty degeneration (macrovesicular steatosis), with occasional ballooning and nuclear pyknosis. The central veins were dilated, and mild sinusoidal congestion was observed. Portal tracts exhibited inflammatory infiltration by mononuclear cells, whereas focal pericentral collagen deposition indicated early fibrosis. Approximately 8 of the 10 diabetic mice demonstrated varying degrees of these histologic alterations. No regenerative nodules or bridging fibrosis were identified.

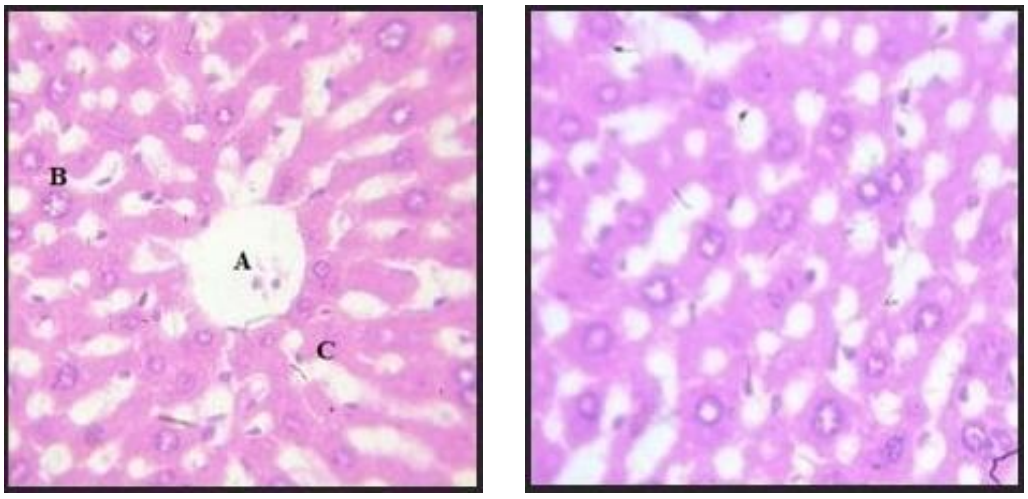


(**a**) (**b**)

Figure 2. Histology of the diabetic untreated group. (**a**) Central vein (A) showing a dilated lumen and surrounding hepatocyte degeneration (B); sinusoids (C) appear congested. (**b**) Pericentral area showing mild collagen deposition (A) and focal inflammatory infiltration (B). H&E × 400.

3.5. Diabetic Kasni-treated

Sections from the Kasni-treated group demonstrated remarkable reversal of diabetic hepatic injury (Figure 3). Hepatocytes exhibited near-normal morphology with reduced cytoplasmic vacuolation and the restoration of regular hepatic cords around a patent central vein. Steatosis and inflammation were minimal, and sinusoidal spaces were comparable to those of the controls. Only 2 of the 10 mice displayed mild residual fatty acid changes. No fibrosis or inflammatory foci were detected. These histological improvements correspond with the observed reduction in blood glucose levels following Kasni extract administration.



(**a**) (**b**)

Figure 3. Histology of the Kasni-treated diabetic group. (**a**) Central vein (A) with organized hepatic plates (B) and normal sinusoidal spaces (C). (**b**) Higher magnification image showing the absence of steatosis and inflammatory infiltrates. H&E × 400.

4. Discussion

The untreated diabetic mice developed both gross and microscopic features of liver injury, including enlargement of the liver and pallor, cytoplasmic vacuolation of liver cells, sinusoidal congestion, and deposition of early pericentral collagen. These histological changes are consistent with diabetes-related steatohepatitis and reflect oxidative and metabolic stress within the liver parenchyma. In contrast, the administration of aqueous Kasni seed extract orally for 28 days significantly improved liver changes in the Kasni treatment group, which presented near-normal hepatic features with the restoration of the central vein, arranged hepatic cords, and the absence of inflammation, steatosis or fibrosis. The gross appearance of the liver was also normal, with restoration of its color, texture, and consistency. These findings highlighted that C. intybus seed extract has a hepatoprotective effect on alloxan-induced diabetic mice, supporting its use as a hepatoprotective agent and an alternative to conventional pharmaceutical agents used for diabetes-related liver pathologies.

Hyperglycemia, the defining feature of DM, plays an important role in hepatic impairment. It causes oxidative stress and inflammation, resulting in histopathological characteristics such as ballooning of hepatocytes, steatosis, dilatation of sinusoids, and fibrosis [36,37]. These metabolic abnormalities may lead to hepatic steatosis, fibrosis, and hepatocellular injury, especially in the absence of blood glucose control [38]. Studies have reported that metabolic abnormalities such as obesity, dyslipidemia, and insulin resistance, which are frequently found in individuals with T2DM, are major contributors to nonalcoholic steatohepatitis (NASH) as well as other chronic liver diseases [39]. Moreover, Li et al. reported that diabetes can lead to nuclear abnormalities in the cells of the liver, including nuclear enlargement, binucleation, and irregularity of chromatin distribution, all of which are features of nuclear stress [40].

Histopathological examination of the liver tissues of diabetic Group B mice treated with saline revealed extensive pathological features, such as hepatic fibrosis, central vein irregularity, distension of the hepatic sinusoids, and intracellular fatty globules within hepatocytes. These are typical characteristics of hepatic steatosis and fibrosis, both of which are typically linked with diabetes-induced liver damage. These results concur with those of Qureshi et al., who examined the role of alloxan in the liver cells of diabetic rats and documented comparable patterns of structural alterations in the central vein as well as in hepatic cells, accompanied by increased fibrosis [41]. Moreover, Dubey et al. reported that diabetic rats exhibit dilated sinusoids as well as increased cellularity of Kupffer cells, features also observed in our control group of diabetic mice [42].

However, in contrast to the results of Groups A or B, in Group C (diabetic mice treated with Kasni), the liver histology showed remarkable recovery. The central vein had a normal structure, the cords of hepatocytes were arranged regularly, and fatty infiltration decreased significantly. Reduced inflammation in hepatic sinusoids as well as the absence of fibrotic zones suggested that treatment with Kasni resulted in histological recovery. These results are in line with earlier observations of the hepatoprotective activity of Kasni. Amirkhani et al. reported that treatment with Kasni restored the normal structure of the central vein, reduced dilation of the sinusoid, and abolished fat globules in liver tissues with oxymetholone toxicity [43]. Additionally, Yadav et al. reported that Kasni protected against carbon tetra chloride-evoked liver injury in rats, verifying its effectiveness in decreasing fibrosis as well as hepatocellular necrosis [44].

The antioxidant and anti-inflammatory activities of the bioactive phytochemicals of Kasni, such as chicoric acid, caffeic acid, and inulin, are also considered to be the reasons for such hepatoprotective actions [45]. Phytochemicals have the capacity to scavenge reactive oxygen species and suppress inflammatory cytokine production, protecting he-

patic cells from oxidative and inflammatory damage [46]. The alignment of hepatic cells and lack of steatosis in the Kasni-treated group are also indicative of the cytoprotective action of Kasni extract in reducing diabetes-related liver damage.

In addition to liver protection, Kasni therapy also caused a reduction in blood glucose in diabetic mice. The antihyperglycemic activity of chicoric acid, the predominant compound in Kasni, supports the results of this study [47]. This dual activity of drugs to control glycemia and protect the liver presents Kasni as an ideal adjunct therapy for diabetes treatment.

The experimental design, use of an alloxan-induced diabetic mouse model, inclusion of both untreated and Kasni-treated groups with a control group, standardized animal handling and dosing protocols, and combination of gross morphological features as well as histopathological analysis to obtain evidence highlight potential strengths of the study. However, the study did not consider biochemical and molecular parameters or liver enzyme profiles, and no statistical analysis was employed to quantify the extent of hepatic recovery. Moreover, the limited sample size may restrict the generalizability and statistical robustness of the findings. Further research with larger groups is needed to substantiate these observations.

5. Conclusions

The findings of this study highlighted that aqueous seed extract of Kasni provides hepatoprotection in alloxan-induced diabetic mice and that treatment with Kasni effectively restored hepatic structures, reduced steatosis and inflammation, and normalized gross liver morphology compared with those of untreated diabetic controls. These findings also suggest that Cichorium intybus has potential as a complementary therapeutic agent for diabetes-related liver injuries.

Author contributions: Conceptualization, MH, and HA; methodology, MH, HA, JS, AR, and ZS; software, MH, and ZS; validation, MH, JS, and AR; formal analysis, MH, and HA; investigation, MH, HA, JS, AR, and ZS; resources, MH, HA, AR, and ZS; data curation, MH; writing—original draft preparation, MH, HA, and JS; writing—review and editing, MH, JS, AR, and ZS; visualization, MH, JS, and AR; supervision, MH; project administration, HA, JS, AR, and ZS. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no specific grant from the public, commercial, or not-for-profit funding agencies.

Ethics statement: This study obtained approval from the Institutional Ethical Review Board of the University of Education (No. UE/IRB/2023/CHEM-011).

Consent to participate: Not Applicable.

Data availability: The data supporting this study's findings are available from the corresponding author, Hamza Asghar, upon reasonable request.

Acknowledgments: None.

Conflicts of interest: The authors declare no conflicts of interest.

References

[1] Eizirik DL, Pasquali L, Cnop M. Pancreatic β-cells in type 1 and type 2 diabetes mellitus: different pathways to failure. Nat Rev Endocrinol. 2020;16:349–62. https://doi.org/10.1038/s41574-020-0355-7

[2] Magliano DJ, Boyko EJ, IDF Diabetes Atlas 10th Edition Scientific Committee. IDF Diabetes Atlas. 10th ed. Brussels: International Diabetes Federation; 2021.

[3] International Diabetes Federation. The Diabetes Atlas. 2024 [cited 10 August 2024]. Available from: https://diabetesatlas.org.

[4] Qian D, Zhang T, Zheng P, Liang Z, Wang S, Xie J, et al. Comparison of oral antidiabetic drugs as add-on treatments in patients with type 2 diabetes uncontrolled on metformin: a network meta-analysis. Diabetes Ther. 2018;9:1945–58. https://doi.org/10.1007/s13300-018-0482-5

[5] Nanditha A, Ma RCW, Ramachandran A, Snehalatha C, Chan JCN, Chia KS, et al. Diabetes in Asia and the Pacific: implications for the global epidemic. Diabetes Care. 2016;39(3):472–85. https://doi.org/10.2337/dc15-1536
[6] Jin Q, Liu T, Qiao Y, Liu D, Yang L, Mao H, et al. Oxidative stress and inflammation in diabetic nephropathy: role of polyphenols. Front Immunol. 2023;14:1185317. https://doi.org/10.3389/fimmu.2023.1185317
[7] Caturano A, D'Angelo M, Mormone A, Russo V, Mollica MP, Salvatore T, et al. Oxidative stress in type 2 diabetes: impacts from pathogenesis to lifestyle modifications. Curr Issues Mol Biol. 2023;45(8):6651–66. https://doi.org/10.3390/cimb45080420
[8] Alam S, Sarker MMR, Sultana TN, Chowdhury MNR, Rashid MA, Chaity NI, et al. Antidiabetic phytochemicals from medicinal plants: prospective candidates for new drug discovery and development. Front Endocrinol. 2022;13:800714. https://doi.org/10.3389/fendo.2022.800714
[9] Singh AK, Kumar P, Rajput VD, Mishra SK, Tiwari KN, Singh AK, et al. Phytochemicals, antioxidant, anti-inflammatory studies, and identification of bioactive compounds using GC–MS of ethanolic novel polyherbal extract. Appl Biochem Biotechnol. 2023;195:4447–68. https://doi.org/10.1007/s12010-023-04363-7
[10] Tran N, Pham B, Le L. Bioactive compounds in anti-diabetic plants: from herbal medicine to modern drug discovery. Biology. 2020;9(9):252. https://doi.org/10.3390/biology9090252
[11] Choudhary S, Kaurav H, Chaudhary G. Kasani beej (Cichorium intybus): Ayurvedic view, folk view, phytochemistry and modern therapeutic uses. Int J Res Appl Sci Biotechnol. 2021;8(2):114-25. https://doi.org/10.31033/ijrasb.8.2.14
[12] Khatoon S. Phytochemistry, pharmacology and Unani traditional uses of Kasni (Cichorium intybus Linn.): a review. J Drug Deliv Ther. 2023;13(6):188-91. https://doi.org/10.22270/jddt.v13i6.6092
[13] Azgomi RND, Karimi A, Tutunchi H, Jazani AM. A comprehensive mechanistic and therapeutic insight into the effect of chicory (Cichorium intybus) supplementation in diabetes mellitus: a systematic review. Int J Clin Pract. 2021;75:e14945. https://doi.org/10.1111/ijcp.14945
[14] Ali A. Herbs that heal: the philanthropic behaviour of nature. Ann Phytomed. 2020;9(1):7–17. https://doi.org/10.21276/ap.2020.9.1.2
[15] de Deus IJ, Martins-Silva AF, Fagundes MM, Paula-Gomes S, Silva FGDe, da Cruz LL, et al. Role of NLRP3 inflammasome and oxidative stress in hepatic insulin resistance and the ameliorative effect of phytochemical intervention. Front Pharmacol. 2023;14:1188829. https://doi.org/10.3389/fphar.2023.1188829
[16] Shen Q, Chen Y, Shi J, Pei C, Chen S, Huang S, et al. Asperuloside alleviates lipid accumulation and inflammation in HFD-induced NAFLD via AMPK signaling pathway and NLRP3 inflammasome. Eur J Pharmacol. 2023;942:175504. https://doi.org/10.1016/j.ejphar.2023.175504
[17] Huang Q, Xin X, Sun Q, An Z, Gou X, Feng Q. Plant-derived bioactive compounds regulate the NLRP3 inflammasome to treat NAFLD. Front Pharmacol. 2022;13:896899. https://doi.org/10.3389/fphar.2022.896899
[18] Zanzabil KZ, Hossain MS, Hasan MK. Diabetes mellitus management: an extensive review of 37 medicinal plants. Diabetology. 2023;4(2):186–234. https://doi.org/10.3390/diabetology4020019
[19] Ignat MV, Coldea TE, Salanță LC, Mudura E. Plants of the spontaneous flora with beneficial action in the management of diabetes, hepatic disorders, and cardiovascular disease. Plants. 2021;10(2):216. https://doi.org/10.3390/plants10020216
[20] Devi Kt R, Sivalingam N. Cichorium intybus attenuates Streptozotocin-induced pancreatic β-cell damage by inhibiting NF-κB activation and oxidative stress. J Appl Biomed. 2020 ;18(2-3):70-9. https://doi.org/10.32725/jab.2020.010
[21] Maleki E, Sadeghpour A, Taherifard E, Izadi B, Pasalar M, Akbari M. The effects of chicory supplementation on liver enzymes and lipid profiles in patients with non-alcoholic fatty liver disease: a systematic review and meta-analysis of clinical evidence. Clin Nutr ESPEN. 2023;55:447–54. https://doi.org/10.1016/j.clnesp.2023.04.025
[22] Saad EA, Hassan HA, Ghoneum MH, El-Dein MA. Edible wild plants, chicory and purslane, alleviated diabetic testicular dysfunction and insulin resistance via suppression of 8OHdG and oxidative stress in rats. PLoS One. 2024;19(4):e0301454. https://doi.org/10.1371/journal.pone.0301454
[23] Yang J, Lei Y, Yan J, Zhong Y, Abudurexiti A, Tan H, et al. Research progress on the homologous effects of Cichorium glandulosum Boiss. et Huet on medicine and food: a review. Nat Prod Commun. 2024;19(4):1934578X241248237. https://doi.org/10.1177/1934578X241248237
[24] Percie du Sert N, Hurst V, Ahluwalia A, Alam S, Avey MT, Baker M, et al. The ARRIVE guidelines 2.0: updated guidelines for reporting animal research. PLoS Biol. 2020;18(7):e3000410. https://doi.org/10.1371/journal.pbio.3000410
[25] Khan B, Ullah A, Khan MA, Amin A, Iqbal M, Khan S et al. Open-access Anti-hyperglycemic and anti-hyperlipidemic effects of a methanolic extract of Debregeasia salicifolia in Alloxan-induced diabetic albino mice. Braz J Biol. 2024;84:e251046. https://doi.org/10.1590/1519-6984.251046
[26] Kim JM. Induction of diabetes mellitus using alloxan in Sprague Dawley rats. Cureus. 2024;16(6):e63359. https://doi.org/10.7759/cureus.63359
[27] Qamar F, Sultana S, Sharma M. Animal models for induction of diabetes and its complications. J Diabetes Metab Disord. 2023;22:1021–28. https://doi.org/10.1007/s40200-023-01277-3
[28] Momoh AO, Fadahunsi AI, Oche VO. The comparative effects of alloxan and streptozotocin in inducement of type-1 diabetes on the intestinal microflora of albino. J Prob Health. 2021;9(8):247.
[29] Queiroz LAD, Assis JB, Guimarães JPT, Sousa ESA, Milhomem AC, Sunahara KKS, et al. Endangered lymphocytes: the effects of alloxan and streptozotocin on immune cells in type 1 induced diabetes. Mediators Inflamm. 2021;2021:9940009. https://doi.org/10.1155/2021/9940009

[30] Bukhari SSI, Abbasi MH, Khan MKA. Dose optimization of alloxan for diabetes in albino mice. Biologia (Pakistan). 2015;61(2): 301–5.
[31] Musaddaq R, Fareed S, Zaid M, Khan A, Zahra M, Shabbir H, et al. Antidiabetic effect of herbal and pharmaceutical interventions on albino mice. Agrobiol Rec. 2024;17:23–9. https://doi.org/10.47278/journal.abr/2024.020
[32] Moloudi MR, Hassanzadeh K, Abdi M, Zandi F, Rahimi K, Izadpanah E. Hepatoprotective effect of the hydroalcoholic extract of Cichorium intybus in a rat model of obstructive cholestasis. Arab J Gastroenterol. 2021;22(1):34–9. https://doi.org/10.1016/j.ajg.2020.08.006
[33] American Veterinary Medical Association. AVMA Guidelines for the Euthanasia of Animals: 2020 Edition. 2020 [cited 10 August 2024]. Available from: https://www.avma.org/sites/default/files/2020-02/Guidelines-on-Euthanasia-2020.pdf.
[34] Suvarna SK, Layton C, Bancroft JD. Bancroft's Theory and practice of histological techniques. 8th ed. Oxford: Elsevier; 2019.
[35] Kleiner DE, Brunt EM, Van Natta M, Behling C, Contos MJ, Cummings OW, et al. Design and validation of a histological scoring system for nonalcoholic fatty liver disease. Hepatology. 2005;41(6):1313-21. https://doi.org/10.1002/hep.20701
[36] Kennedy MC, Dinneen SF. Management of type 1 diabetes mellitus. Medicine. 2010;38(11):610–17. https://doi.org/10.1016/j.mpmed.2010.08.002
[37] Smirne C, Croce E, Di Benedetto D, Cantaluppi V, Comi C, Sainaghi PP, et al. Oxidative stress in non-alcoholic fatty liver disease. Livers. 2022;2(1):30-76. https://doi.org/10.3390/livers2010003
[38] Gjorgjieva M, Mithieux G, Rajas F. Hepatic stress associated with pathologies characterized by disturbed glucose production. Cell Stress. 2019;3(3):86–99. https://doi.org/10.15698/cst2019.03.179
[39] Kim H, Lee DS, An TH, Park HJ, Kim WK, Bae KH, et al. Metabolic spectrum of liver failure in type 2 diabetes and obesity: from NAFLD to NASH to HCC. Int J Mol Sci. 2021;22(9):4495. https://doi.org/10.3390/ijms22094495
[40] Li B, Hussain W, Jiang ZL, Wang JY, Hussain S, Yasoob TB, et al. Nuclear proteins and diabetic retinopathy: a review. Biomed Eng Online. 2024;23:62. https://doi.org/10.1186/s12938-024-01258-4
[41] Qureshi AS, Ghaffor J, Usman M, Ehsan N, Umar Z, Sarfraz A. Effect of ethanolic preparations of cinnamon (Cinnamomum zeylanicum) extract on hematologic and histometric parameters of selected organs in Alloxan® induced diabetic female albino rats. J Diabetes Metab Disord. 2019;18(2):505–12. https://doi.org/10.1007/s40200-019-00457-4
[42] Dubey SK, Yadav C, Bajpeyee A, Singh MP. Effect of Pleurotus fossulatus aqueous extract on biochemical properties of liver and kidney in streptozotocin-induced diabetic rat. Diabetes Metab Syndr Obes. 2020;13:3035–46. https://doi.org/10.2147/DMSO.S265798
[43] Amirkhani R, Farzaei MH, Ghanbari E, Khazaei M, Aneva I. Cichorium intybus improves hepatic complications induced by oxymetholone: an animal study. J Med Plants By-Products. 2022;11(1):111–8. https://doi.org/10.22092/jmpb.2021.354093.1347
[44] Yadav A, Tiwari NN, Srivastava SP, Tripathi SM, Mishra S. Bioactive compound containing hepatoprotective activity. Curr Bioact Compd. 2023;19(9):33–40. https://doi.org/10.2174/1573407219666230411111304
[45] Azay-Milhau J, Ferrare K, Leroy J, Aubaterre J, Tournier M, Lajoix AD, et al. Antihyperglycemic effect of a natural chicoric acid extract of chicory (Cichorium intybus L.): a comparative in vitro study with the effects of caffeic and ferulic acids. J Ethnopharmacol. 2013;150(2):755–60. https://doi.org/10.1016/j.jep.2013.09.046
[46] Venmathi Maran BA, Iqbal M, Gangadaran P, Ahn BC, Rao PV, Shah MD. Hepatoprotective potential of Malaysian medicinal plants: a review on phytochemicals, oxidative stress, and antioxidant mechanisms. Molecules. 2022;27(5):1533. https://doi.org/10.3390/molecules27051533
[47] Anju, Javed G, Javaid R, Ahmed F. Kasni (Cichorium intybus): a Unani hepatoprotective drug. J Drug Deliv Ther. 2020;10(4):238-41. https://doi.org/10.22270/jddt.v10i4.4162

Bulletin of
Pharmaceutical & Medicinal Research

Original Article

Therapeutic effects of kaempferol, quercetin and quinoa seed extract on high-fructose diet-induced hepatic and pancreatic alterations in diabetic rats

Sania Jamal [a], Aisha Tahir [b,*], Junaid Ali Khan [a]

[a] Department of Physiology and Pharmacology, University of Agriculture, Pakistan
[b] Department of Biochemistry, University of Health Sciences, Pakistan

* Correspondence: aishatahir85@gmail.com

Citation: Jamal S, Tahir A, Khan JA. Therapeutic effects of kaempferol, quercetin and quinoa seed extract on high-fructose diet-induced hepatic and pancreatic alterations in diabetic rats. Bull Pharm Med Res. 2024;2:15-25.

Received: 15 October 2024
Revised: 17 December 2024
Accepted: 24 December 2024
Published: 31 December 2024

Publisher's Note: Logixs Journals remains neutral concerning jurisdictional claims in its published subject matter, including maps and institutional affiliations.

Abstract

Excess fructose intake is a main contributor to metabolic syndrome, which causes dyslipidemia, nonalcoholic fatty liver disease (NAFLD) and insulin resistance. The present study examined the protective effects of quercetin, quinoa seed extract (QSE), and kaempferol against high-fructose diet (HFrD)-induced pancreatic and hepatic alterations in Wistar albino rats. Thirty rats were divided into six groups (n = 5, each group consisted of 5 rats): the control group, HFrD + metformin group, HFrD + kaempferol group, HFrD + quercetin group, and HFrD + QSE group. Treatments were administered orally for 21 days following induction with 61% fructose. Biochemical function tests were performed for hemoglobin (Hb) and alanine aminotransferase (ALT) levels, and histopathological analyses of hepatic and pancreatic architecture were performed. The results showed that HFrD intake significantly increased ALT levels and body weight, accompanied by hepatocellular degeneration and inflammatory changes in pancreatic β-cells. Kaempferol, quercetin, and QSE administration significantly increased the Hb concentration, decreased ALT activity, and reduced vacuolar degeneration and hepatic necrosis. Kaempferol and quercetin resulted in nearly normal hepatocyte morphology among the test compounds, while QSE resulted in the greatest decrease in net weight gain. In the treated groups, pancreatic sections revealed the integrity of the islets of Langerhans and decreased inflammation of the islets. This study demonstrated that flavonoids from plants and the QSE have hepatoprotective and pancreatic protective effects through antioxidant and anti-inflammatory mechanisms; hence, these compounds are potentially useful as therapeutic agents in the management of fructose-induced metabolic dysfunctions.

Keywords

Kaempferol; Quinoa seed extract; Quercetin; Pancreatic and pancreatic protection; High-fructose diet

1. Introduction

Metabolic syndrome, a medical condition worldwide, is generally associated with diabetes mellitus (DM), insulin resistance, dyslipidemia, and increased triglyceride and cholesterol levels, which are often accompanied by liver and pancreas dysfunction [1]. Excessive fructose intake is one of the contributing factors to type 2 diabetes mellitus (T2DM). High fructose intake causes oxidative stress and inflammation in pancreatic beta cells, leading to impaired insulin production and secretion, thus causing hyperglycemia [2]. Excess fructose intake contributes to visceral adipose deposition and hepatic steatosis to promote the production of inflammatory mediators, increasing the risk of chronic diseases such as T2DM and nonalcoholic fatty liver disease (NAFLD) [3]. NAFLD,

a disease characterized by fat deposition on hepatocytes, is associated with an abnormal lipid profile, including low-density lipoprotein (LDL) and high cholesterol levels [4]. Biomarkers such as aspartate aminotransferase (AST) and alkaline phosphatase (ALP) increase due to hepatocellular injury. Chronic fructose consumption significantly contributes to cirrhosis, hypertriglyceridemia and NAFLD [5].

Pakistan ranks third in the world in terms of diabetes prevalence, followed by China and India. The national prevalence of diabetes has consistently increased over recent years, increasing from 11.77% in 2016 to 16.98% in 2018 and 17.1% in 2019 [6]. According to the latest International Diabetes Foundation (IDF) atlas in 2023, approximately 33 million adults are living with T2DM in Pakistan, making it the third-largest population with diabetes in the world. In addition, approximately 11 million adults have impaired glucose tolerance, placing them at high risk of progression to diabetes, whereas approximately 8.9 million people with diabetes are still undiagnosed [7]. The variability in the prevalence of gestational diabetes mellitus (GDM) in Pakistani people is also reflected by its wide range, ranging from 4.41% to 57.90%, across different studies [8].

The therapeutic potential of medicinal plants has gained increased scientific attention. Bioactive plant constituents such as kaempferol have shown beneficial effects on hypertension, pancreatic disorders, and DM [9]. Flavonoids are naturally occurring polyphenolic compounds that are widely distributed among vegetables and fruits, including radish, parsley, grains, oregano, leafy greens, and citrus fruits such as oligomers, aglycones and glucosides [10]. Glucosides include quercetin, naringin, kaempferol, and hesperidin [11].

Among these, the most powerful hepatoprotective and antidiabetic properties are exhibited by kaempferol and quercetin. Quercetin is involved in reducing pancreatic inflammation, which moderates Carnitine palmitoyltransferase I (CPT-1) expression to increase fatty acid oxidation, thereby reducing NAFLD progression [12]. Kaempferol stabilizes normal liver function by inhibiting inflammatory mediators and reducing hepatic triglyceride accumulation through the downregulation of peroxisome proliferator-activated receptors (PPAR) and sterol regulatory element binding transcription factor 1 (SREBP-1) [13]. Quercetin offers further protective benefits against metabolic syndrome, liver cancer, and cardiovascular disease by suppressing NF-κB activation and reducing the secretion of proinflammatory cytokines such as IL-6, TNF-α and IL-1α [14,15]. Flavonoids have been demonstrated to be effective antidiabetic therapeutic agents because they protect pancreatic beta-cell integrity and support glucose homeostasis. In type 1 diabetes mellitus (T1DM), autoimmune beta-cell destruction results in high blood sugar levels, whereas long-standing insulin resistance contributes to T2DM [16]. Kaempferol and quercetin protect beta cells from apoptosis. Kaempferol has been shown to specifically inhibit the activity of caspase-3 [17].

Chenopodium quinoa Willd. (Chenopodiaceae) consists of approximately 250 species that are spread all over the world. Owing to its gluten-free nature, quinoa is consumed by patients suffering from celiac disease and is considered highly nutritious. Quinoa seed extract (QSE) includes various flavanols, such as kaempferol glycosides, apigenin and quercetin [18]. QSE improves the lipid profile, mineral balance, protein metabolism, and blood glucose regulation [19]. It has been shown to lower total cholesterol, triglyceride, LDL, blood sugar, and circulating protein levels [20]. Therefore, this study aimed to compare the effects of standard therapy (metformin) and natural compounds (quercetin, kaempferol, and QSE) on metabolic syndrome and to evaluate the protective effects of these compounds against high-fructose diet (HFrD)-induced hepatic and pancreatic alterations.

2. Materials and methods

2.1. Study design and approval

This experimental study was approved by the Directorate of Graduate Studies, University of Agriculture, Faisalabad (No. 5738-27/DGS). The study was based on an animal model; young albino Wistar rats were obtained from Government College University, Faisalabad, and the study was conducted at the Institute of Physiology and Pharmacology, University of Agriculture Faisalabad, Pakistan.

2.2. Selection of drugs

Kaempferol and quercetin were selected as representative pure flavonoids because of their well-documented antidiabetic, antioxidant, and hepatoprotective activities, including the modulation of insulin signaling, lipid metabolism, and pancreatic β-cell protection [21,22]. QSE was included to assess the synergistic effects of multiple phytochemicals naturally present in quinoa, particularly kaempferol and quercetin glycosides, which may act additively or synergistically to enhance therapeutic outcomes [23]. The comparative evaluation of these pure compounds and a whole-plant extract allow a broader assessment of both isolated bioactive molecules and complex phytochemical mixtures in mitigating high-fructose diet (HFrD)-induced hepatic and pancreatic alterations.

2.3. Collection of drugs and chemicals

All the compounds were prepared in vehicle dimethyl sulfoxide (DMSO, 250 µL) diluted with 60% distilled water for administration. Metformin (chemical formula $C_4H_{11}N_5$, molar mass ~129.1 g/mol) is a first-line medication for T2DM and was obtained commercially under the name Glucophage. Quercetin and kaempferol were obtained from commercial sources [24]. Quinoa seeds were sourced and extracted via standard solvent extraction methods [25]. D-fructose (Sigma–Aldrich) was purchased to induce HFrD.

2.4. Experimental grouping

This study involved 30 albino Wistar rats weighing 150–200 grams. Thirty rats were divided into 6 groups (n = 5 per group). Group 1 served as the control group and was given a standard diet. Group 2 served as the disease model (HFrD 61% only). Group 3 received HFrD + metformin (M) (HFrD + M, 61% fructose + 100 mg/kg body weight, orally). Group 4 received HFrD + kaempferol (K) (HFrD + K, 61% fructose + 100 mg/kg). Group 5 received HFrD + quercetin (Q) (HFrD + Q, 61% fructose + 100 mg/kg). Group 6 received HFrD + QSE (HFrD + QSE, 61% fructose + 200 mg/kg). All the treatments were given orally.

2.5. Administration of drugs

In the first week of the study, a HFrD was given to all the groups except the control group (which was fed a normal diet and received no treatment). Drug administration was initiated in the second week. Kaempferol, quercetin, and QSE were administered to the respective treatment groups (HFrD + K, HFrD + Q, and HFrD + QSE) via oral gavage for 3 weeks. All the compounds were delivered in 250 µL of DMSO diluted with 60% distilled water. The treatments were given daily, and the experiment lasted a total of 28 days. The body weights of all the rats were measured daily throughout the 28 days. On day 29 of the trial, the animals were euthanized for sample collection; blood samples and liver and pancreas organs were collected from all 6 groups in accordance with ethical guidelines.

2.6. Data collection procedure

The rats were anesthetized via the inhalation of chloroform via cotton swabs. Under deep anesthesia, an incision was made in the left jugular vein to collect a blood sample (~2 mL) in an EDTA vial for complete blood count (CBC) analysis. The remaining blood was collected into clot activator (red-top) tubes to obtain serum for biochemical analyses [alanine aminotransferase (ALT) and AST levels]. After dissection, the liver and pancreas from each rat were harvested and placed in 10% neutral buffered formalin for preservation.

2.7. Histopathological analysis

Liver and pancreas tissue samples were fixed in 10% neutral buffered formalin and then processed through graded ethanol for dehydration. Xylene was used to clear the tissues, which were then embedded in paraffin wax. Five-micrometer-thick sections were cut via a microtome. Hematoxylin and eosin (H&E) staining was performed following standard protocols. The stained sections were mounted and examined via light microscopy for histopathological changes.

2.8. Statistical analysis

Descriptive statistics [mean ± standard error (SE)] were calculated for body weight, white blood cell (WBC) count, and hemoglobin (Hb), ALT, and AST levels for each group via SPSS version 24.00.

3. Results

Table 1 shows that the terminal average weight of all six groups was greater than the initial average weight. Minimal weight gain was observed in all groups during the first week; however, weight increased in the second week and continued to rise throughout the trial. The groups receiving kaempferol, quercetin, or QSE gained less body weight than the untreated HFrD group did. Moreover, the HFrD + QSE group presented the lowest net weight gain over the course of the experiment. Compared with the control group, the HFrD group presented the greatest weight gain, whereas the HFrD + QSE group presented the smallest weight gain.

Table 1. Weekly average body weights (in grams) of the rats measured during the four-week experimental period.

Days	Control	HFrD	HFrD + M	HFrD + K	HFrD + Q	HFrD + QSE
	Mean ± SE	Mean ± SE	Mean ± SE	Mean ± SE	Mean ± SE	Mean ± SE
			1st Week			
1	175.4 ± 1.2	186.8 ± 1.4	183.0 ± 0.5	174.2 ± 0.6	156.8 ± 0.5	203.6 ± 1.7
2	174.6 ± 1.1	185.6 ± 1.4	183.2 ± 0.5	175.6 ± 0.6	152.0 ± 0.5	194.2 ± 1.7
3	178.0 ± 1.1	186.2 ± 1.4	184.8 ± 0.6	177.0 ± 0.6	158.4 ± 0.5	197.2 ± 1.7
4	178.8 ± 1.1	186.0 ± 1.4	189.0 ± 0.7	178.2 ± 0.6	161.4 ± 0.5	195.2 ± 1.6
5	180.4 ± 1.1	188.4 ± 1.4	191.2 ± 0.6	179.8 ± 0.6	164.0 ± 0.5	197.6 ± 1.6
6	179.4 ± 1.0	188.0 ± 1.4	191.6 ± 0.6	180.4 ± 0.7	165.4 ± 0.5	199.2 ± 1.6
7	180.6 ± 1.0	184.8 ± 1.4	187.8 ± 0.6	184.2 ± 0.6	163.8 ± 0.5	197.8 ± 1.8
			2nd Week			
8	188.6 ± 0.9	186.6 ± 1.4	192.0 ± 0.6	183.8 ± 0.6	163.8 ± 0.5	194.8 ± 1.7
9	194.0 ± 0.8	204.4 ± 1.3	205.6 ± 0.6	199.6 ± 0.7	188.0 ± 0.4	210.6 ± 1.7
10	185.2 ± 0.9	186.2 ± 1.4	196.0 ± 0.6	183.6 ± 0.6	171.8 ± 0.4	202.4 ± 1.7
11	187.4 ± 0.8	190.8 ± 1.4	200.2 ± 0.7	186.8 ± 0.6	182.8 ± 0.5	203.4 ± 1.7

Days	Control	HFrD	HFrD + M	HFrD + K	HFrD + Q	HFrD + QSE
	Mean ± SE	**Mean ± SE**	**Mean ± SE**	**Mean ± SE**	**Mean ± SE**	**Mean ± SE**
12	196.4 ± 0.8	202.8 ± 1.3	193.8 ± 1.1	194.6 ± 0.7	186.8 ± 0.4	209.4 ± 1.6
13	194.0 ± 0.8	204.4 ± 1.3	205.6 ± 0.6	199.6 ± 0.7	188.0 ± 0.4	210.6 ± 1.7
14	196.8 ± 0.7	212.2 ± 1.2	210.6 ± 0.6	213.0 ± 0.6	190.0 ± 0.4	213.0 ± 1.5
			3rd Week			
15	197.6 ± 0.7	210.0 ± 1.2	212.2 ± 0.6	216.6 ± 0.6	189.4 ± 0.5	222.6 ± 1.5
16	205.0 ± 0.7	211.0 ± 1.1	208.2 ± 0.7	217.4 ± 0.6	189.2 ± 0.4	219.6 ± 1.5
17	208.6 ± 0.7	216.2 ± 1.3	210.0 ± 0.7	212.0 ± 0.6	188.6 ± 0.5	228.2 ± 1.6
18	209.2 ± 0.7	215.8 ± 1.2	210.2 ± 0.6	208.8 ± 0.6	192.2 ± 0.5	227.4 ± 1.5
19	209.8 ± 0.7	216.8 ± 1.3	211.4 ± 0.6	210.4 ± 0.6	194.4 ± 0.5	229.6 ± 1.5
20	209.0 ± 0.7	235.0 ± 1.1	218.6 ± 0.6	224.8 ± 0.3	192.8 ± 0.5	239.6 ± 1.6
21	210.4 ± 0.7	234.8 ± 1.2	217.6 ± 0.6	219.4 ± 0.5	191.4 ± 0.5	238.2 ± 1.6
			4th Week			
22	214.2 ± 0.7	239.6 ± 1.2	219.2 ± 0.6	220.0 ± 0.6	199.4 ± 0.6	240.4 ± 1.6
23	216.0 ± 0.7	244.8 ± 1.2	222.6 ± 0.6	217.6 ± 0.5	198.2 ± 0.6	240.8 ± 1.6
24	216.0 ± 0.7	245.4 ± 1.2	222.8 ± 0.6	217.6 ± 0.5	198.8 ± 0.6	241.4 ± 1.6
25	216.8 ± 0.7	245.6 ± 1.2	223.0 ± 0.6	218.0 ± 0.5	199.4 ± 0.6	242.0 ± 1.6
26	218.6 ± 0.6	237.2 ± 1.2	221.6 ± 0.6	212.4 ± 0.6	198.4 ± 0.6	241.6 ± 1.6
27	219.8 ± 0.6	231.2 ± 1.2	220.8 ± 0.5	212.0 ± 0.6	200.6 ± 0.6	238.6 ± 1.6
28	219.2 ± 0.6	231.8 ± 1.1	218.0 ± 0.5	213.2 ± 0.6	199.0 ± 0.5	234.0 ± 1.5

Abbreviations: HFrD, high-fructose diet; M, metformin; K, kaempferol; Q, quercetin; QSE, quinoa seed extract.

Compared with the control group, the HFrD group presented a mild increase in leukocyte count, with an average of 11.98 ± 2.97 × 10^3/μL, with an average of 9.80 ± 1.13 × 10^3/μL. These findings suggest that systemic inflammation coexists with metabolic stress (Table 2). Moreover, Hb concentrations were slightly lower in the HFrD group, with an average of 147.73±23.80 g/L, than in the control group, which was 154.07 ± 9.85 g/L. This reduction in Hb and leukocyte levels is consistent with anemia observed in DIDM (diet-induced diabetic models). Furthermore, the markers of liver function were significantly greater in the HFrD group; ALT and AST increased to 104.41 ± 31.04 U/L and 75.02 ± 13.93 U/L, respectively. The values for ALT and AST in the control group were 71.25 ± 10.54 U/L and 68.03 ± 6.46 U/L, respectively. These increases reflect hepatocellular damage due to excess fructose.

Quercetin (HFrD + Q) and kaempferol (HFrD + K) treatment significantly diminished these abnormalities. Both flavonoids resulted in ALT and AST levels close to normal, with ALT values recorded at 64.30 ± 9.14 U/L for HFrD + K and 64.41 ± 13.81 U/L for HFrD + Q and AST values of 59.26 ± 4.09 U/L for HFrD + K and 60.49 ± 9.70 U/L for HFrD + Q. These findings indicate that the effective hepatoprotective actions of these compounds occur through anti-inflammatory and antioxidant mechanisms. Additionally, the Hb levels showed partial recovery, measuring 126.93 ± 31.18 g/L in the HFrD + K group and 142.53 ± 22.10 g/L in the HFrD + Q group. The group that received HFrD + QSE (quinoa seed extract) presented similar trends, with progress in enzymatic and hematological profiles. Specifically, the Hb level was 113.20 ± 62.50 g/L, the ALT level was 88.22 ± 28.25 U/L, and the AST level was 57.46 ± 4.52 U/L. These results revealed the micronutrient and antioxidant benefits of the QSE matrix. Comparable stabilization was attained by treatment with metformin (HFrD + M), confirming a response to therapy in this model.

Table 2. White blood cells (WBCs) count, hemoglobin (Hb), and serum AST and ALT levels across experimental groups.

Groups	WBCs (×10^3/μL)	Hb (g/L)	ALT (U/L)	AST (U/L)
	Mean ± SE	Mean ± SE	Mean ± SE	Mean ± SE
Control	9.80 ± 1.13	154.07 ± 9.85	71.25 ± 10.54	68.03 ± 6.46
HFrD	11.98 ± 2.97	147.73 ± 23.80	104.41 ± 31.04	75.02 ± 13.93
HFrD + M	9.36 ± 2.64	134.67 ± 11.16	87.84 ± 40.82	65.40 ± 14.59
HFrD + K	13.20 ± 2.26	126.93 ± 31.18	64.30 ± 9.14	59.26 ± 4.09
HFrD + Q	10.50 ± 3.16	142.53 ± 22.10	64.41 ± 13.81	60.49 ± 9.70
HFrD + QSE	11.18 ± 1.59	113.20 ± 62.50	88.22 ± 28.25	57.46 ± 4.52

Abbreviations: Hb = hemoglobin; HFrD, high-fructose diet; M, metformin; K, kaempferol; Q, quercetin; QSE, quinoa seed extract.

Microscopic examination of the tissue slides revealed that hepatocytes in the control group appeared nearly normal, with a typical arrangement of hepatic cords (Figure 1).

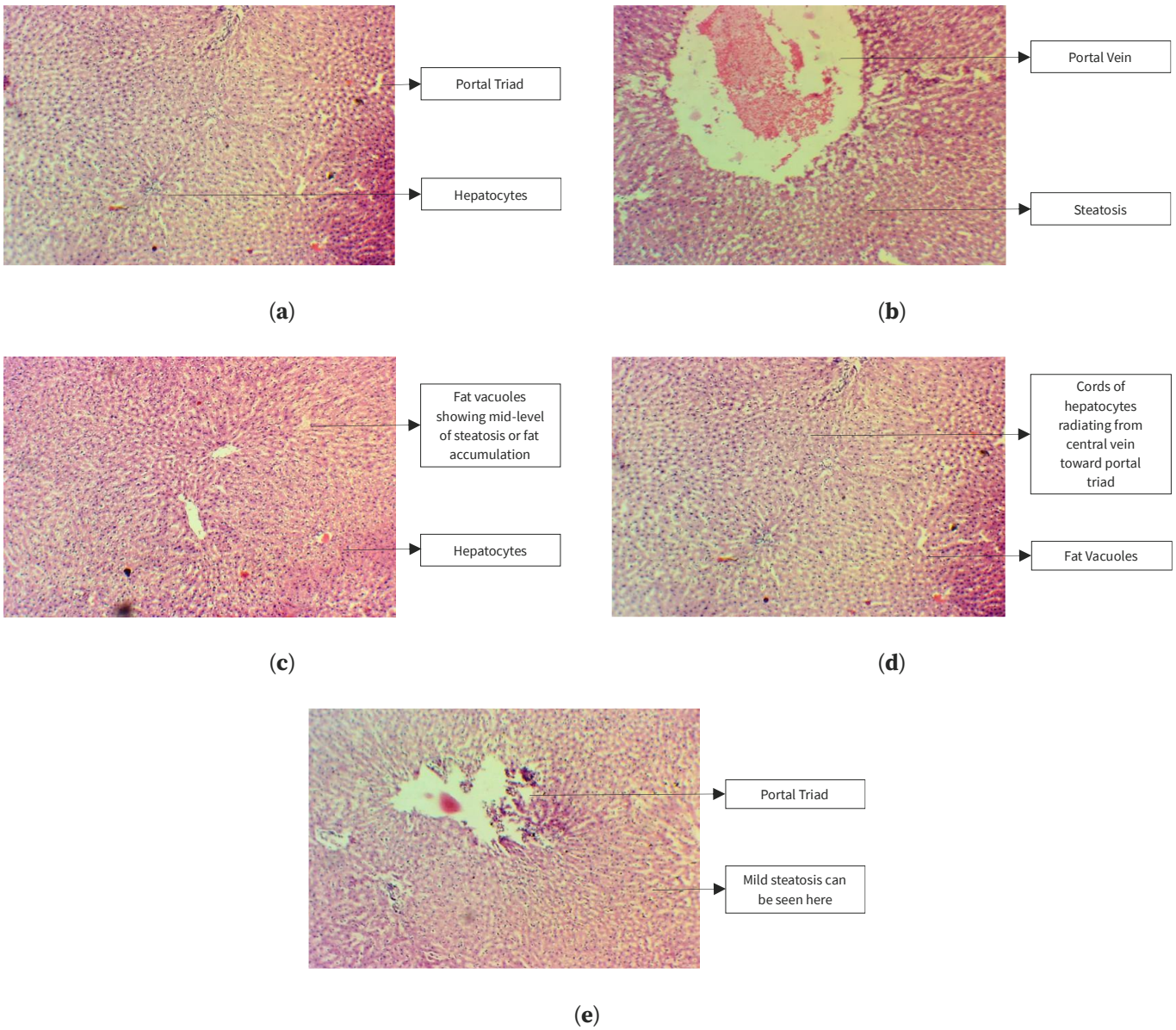


Figure 1. Histopathological analysis of livers from the control group (a), HFrD group (b), kaempferol-treated group (c), quercetin-treated group (d), and QSE-treated group (e).

In contrast, the HFrD group presented signs of vacuolar degeneration in hepatocytes, dilated central veins and sinusoids, and hepatocellular necrosis. However, the groups treated with kaempferol, quercetin, or QSE along with HFrD presented only mild vacuolar degeneration, along with some dilated sinusoids and central veins, indicating the therapeutic effects of these plant flavonoids against HFrD-induced hepatotoxicity. Focal hepatic lesions (degeneration and necrosis with infiltration of WBCs) were observed in the HFrD group but were markedly reduced in the treated groups.

Histopathological analysis of pancreatic tissue samples revealed that the control group exhibited a normal arrangement of beta cells within the islets of Langerhans (Figure 2). In contrast, the HFrD group displayed inflammation of beta cells and abnormal enlargement of the islets, along with edema and dilated blood vessels in the pancreatic tissue. However, these adverse effects were reversed in the groups treated with kaempferol, quercetin, or QSE, with the pancreatic islet architecture preserved and reduced signs of inflammation and degeneration, thereby mitigating the metabolic disorders and pancreatic damage caused by HFrD.

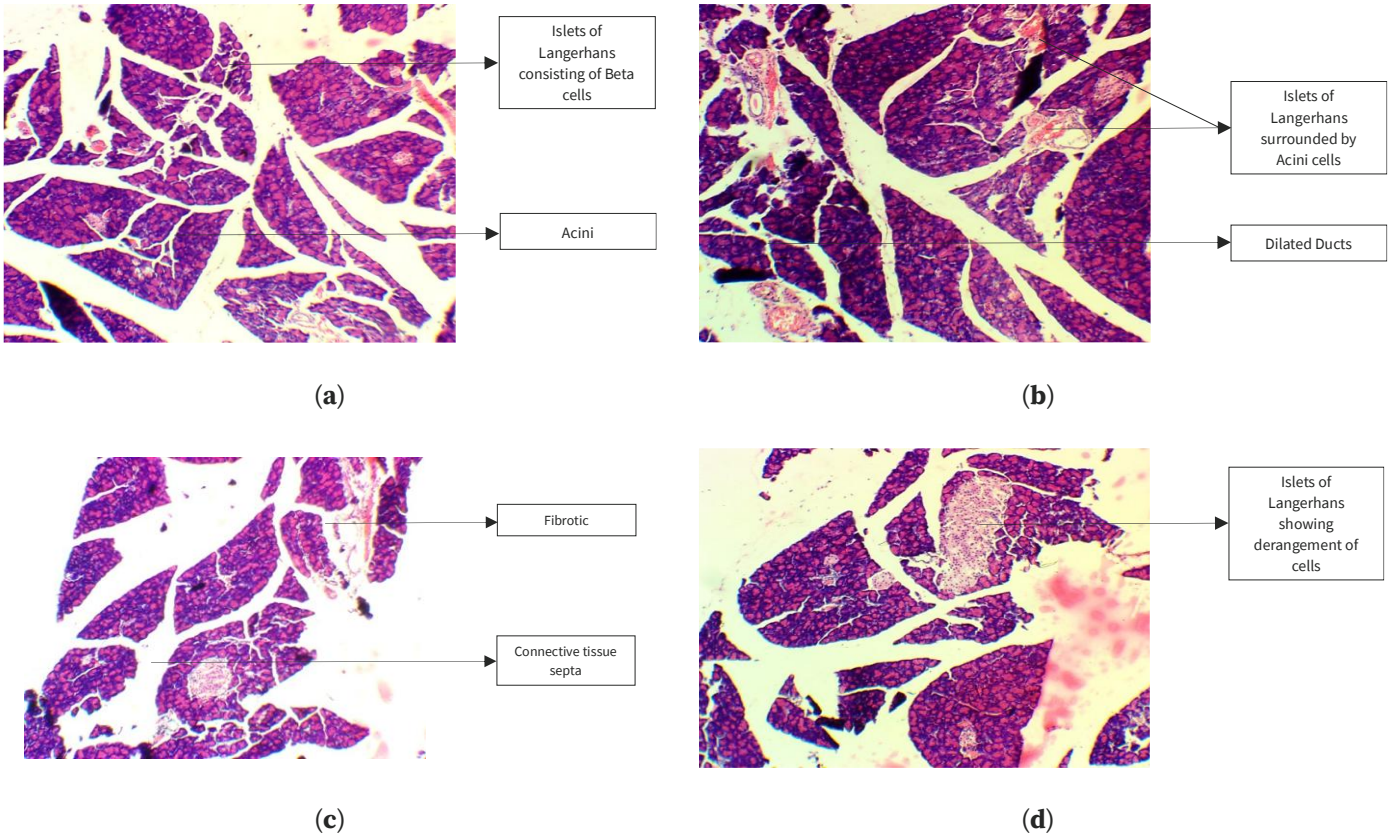


Figure 2. Histopathological analysis of the pancreas in the control group (a), HFrD group (b), kaempferol-treated group (c), and quercetin-treated group (d).

4. Discussion

Taken together, all the treated groups showed a protective trend in comparison with the HFrD-untreated group. Body weight increased progressively in all groups during the experimental period, but its magnitude of increase was significantly lower in the groups receiving kaempferol, quercetin, or QSE, with the lowest net increase being observed in the HFrD + QSE group. Systemic metabolic stress due to HFrD feeding resulted in decreased Hb levels in rats in the HFrD group, while partial recovery of its concentration was observed in the treatment groups, suggesting partial correction of metabolic imbal-

ance. Serum ALT activity, an important biomarker of hepatocellular injury, was highly elevated in HFrD rats, while the administration of kaempferol, quercetin, or QSE resulted in a remarkable reduction in ALT levels in these groups of rats and, in some instances, a decrease in ALT levels compared with the respective control values. Histopathological examinations further confirmed the above biochemical observations. HFrD exposure resulted in vacuolar degeneration, hepatocellular necrosis and inflammatory infiltration in liver tissues, whereas the treated groups exhibited only mild degenerative changes in the hepatic tissues with preserved architecture of the liver. Similarly, tissues of the pancreas obtained from diabetic rats fed a showed inflammation of the islets of Langerhans, disruption of β-cells, and edema, whereas those in the treatment groups maintained a normal islet morphology with fewer inflammatory changes. Overall, these observations suggested that quercetin, kaempferol, and QSE had significant pancreatic protective effects by decreasing fructose-induced structural and metabolic changes in diabetic rats.

Several studies have reported that flavonoids attenuate diet-induced weight gain. Kaempferol supplementation reduces weight gain and adiposity in rodent models by modulating the gut microbiota, increasing energy expenditure and improving insulin sensitivity, which is consistent with our observation of lower net weight gain in kaempferol-treated rats [26,27]. Quercetin has repeatedly been shown to blunt body weight gain in high-fat or fructose feeding regimens by reducing adipogenesis and increasing fatty acid oxidation (AMPK/SIRT1 pathways), which supports our quercetin group's reduced weight gain relative to that of untreated HFrD animals [28,29]. Studies of quinoa or quinoa-derived extracts report reductions in weight gain or adiposity or improvements in metabolic indices versus obesogenic diets; these effects are attributed to combined polyphenol, fiber and protein contents, which can modulate satiety, lipid metabolism and the gut microbiota, which is compatible with our finding that QSE produces the smallest net weight gain [30,31].

Chronic high-fructose diets have been linked to dysregulated iron metabolism and systemic inflammation in animal models, which can manifest as reduced Hb or altered iron handling; one study of prolonged fructose exposure described inflammation-linked dysregulation of iron homeostasis in rats, providing a plausible mechanism for reduced Hb after HFrD [32]. Oxidative damage to erythrocytes under metabolic stress (high fructose/NAFLD) has been documented; antioxidants such as quercetin reduce erythrocyte oxidative markers and protect membrane integrity, which can help preserve Hb concentration or reduce hemolysis—this aligns with the partial Hb recovery observed in flavonoid-treated groups [33]. Reviews of red blood cell (RBC) redox biology emphasize that systemic metabolic stressors (lipid peroxidation, inflammation) impair RBC antioxidant systems and may lower Hb indirectly; interventions that restore redox balance can partially reverse these effects [34].

HFrD (and combined high-fat/high-fructose diets) consistently increase transaminase and liver injury marker levels in rodents and are widely used to model NAFLD/non-alcoholic steatohepatitis (NASH); this finding replicates the marked ALT elevation observed in the HFrD group [35]. Multiple recent preclinical reports have shown strong hepatoprotective effects of quercetin, with reductions in ALT/AST, improvements in histology, and normalization of lipid metabolism attributed to antioxidant, anti-inflammatory and autophagy-promoting actions (AMPK/mitophagy pathways), which is consistent with our quercetin group's ALT normalization [36]. Kaempferol has been shown to reduce ALT and attenuate hepatic inflammation in NASH and chemical injury models (e.g., suppression of the NLRP3 inflammasome/caspase-3 pathway), which is consistent with the pronounced decrease in ALT observed in the kaempferol group [37].

Diets high in fructose cause hepatic steatosis and inflammatory and advanced levels of necrosis and fibrosis; the histological patterns you observed are typical of HFrD models and have been reproduced in multiple recent studies [38]. Quercetin treatment reduces lipid droplet accumulation, hepatocyte ballooning and inflammatory cell infiltration in NAFLD models; mechanistic studies have revealed reduced SREBP-1c/fatty acid synthase expression (FASN) expression, increased PPARα-mediated β-oxidation, and improved mitochondrial function/mitophagy, which aligns with improvements in histology [36]. Kaempferol has been shown to decrease lipid accumulation, oxidative damage and inflammatory signaling in the liver, including histological amelioration in NASH models (reduced steatosis and necrosis), supporting the protective effects of kaempferol [26,37,39].

High-fructose feeding leads to systemic insulin resistance, β-cell stress and, in some models, β-cell dysfunction and islet inflammation; several animal studies have shown islet hypertrophy/hyperplasia or inflammatory changes in response to prolonged dietary sugar overload, which is consistent with the histology of the HFrD group [35,40]. Quercetin protects pancreatic β-cells from oxidative stress and apoptosis via the activation of Sirt3 and other antioxidant pathways, reducing cytokine-induced damage and preserving insulin secretion capacity—these findings align with the preserved islet morphology observed in the quercetin group [33,41]. Kaempferol stimulates autophagy, mitigates β-cell lipotoxicity via AMPK/mTOR signaling and supports β-cell survival in diabetic models; recent mechanistic and metabolomic studies reported that kaempferol improved islet histology and function, which is consistent with our kaempferol group's ability to preserve islets [38,39].

The main strength of the current study is its controlled experimental design, which allowed the investigation of pancreatic and hepatic changes via biochemical markers as well as comprehensive tissue examination. A comparable evaluation of two pure flavonoids with a natural extract provides a practical basis for comparing their therapeutic potential. The use of valid biomarkers, such as AST and ALT, and standardized histological scoring in the current study also increases the confidence of the results. However, these experiments were conducted with relatively few animals, and the animal model was unable to fully represent the multiple inflammatory and metabolic mechanisms linked with human diabetes. In addition, single-dose regimens for each compound were adopted, and no attempt was made to understand dose–response relationships. Moreover, no advanced statistics are employed in the study. Larger sample sizes, multiple dosing schemes, and mechanistic analyses at the molecular level are needed in future studies to increase the translational relevance of these findings.

5. Conclusions

QSE, quercetin and kaempferol can mitigate the pancreatic and hepatic changes induced in high-fructose diet-fed diabetic rats by improving biochemical markers, preserving tissue architecture, and reducing degenerative and inflammatory changes. The benefits observed in this model are very likely mediated through antioxidant pathways and metabolic regulatory pathways. In general, the results suggest that these bioactive phytochemicals represent potential therapeutic approaches as complementary agents in the prevention or management of diabetes-related hepatic-pancreatic dysfunction.

Author contributions: Conceptualization, SJ, AT, and JAK; methodology, SJ, and AT; software, SJ, and AT; validation, AT; formal analysis, SJ; investigation, SJ, and AT; resources, SJ, and JAK; data curation, SJ; writing—original draft preparation, SJ, and AT; writing—review and editing, SJ, AT, and JAK; visualization, AT; supervision, JAK; project administration, JAK. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no specific grant from the public, commercial, or not-for-profit funding agencies.

Ethics statement: This study was approved by the Directorate of Graduate Studies, University of Agriculture, Faisalabad (No. 5738-27/DGS).

Consent to participate: Not Applicable.

Data availability: The data supporting this study's findings are available from the corresponding author, Aisha Tahir, upon reasonable request.

Acknowledgments: None.

Conflicts of interest: The authors declare no conflicts of interest.

References

[1] Al-Qabba MM, El-Mowafy MA, Althwab SA, Alfheeaid HA, Aljutaily T, Barakat H. Phenolic profile, antioxidant activity, and ameliorating efficacy of Chenopodium quinoa sprouts against CCl4-induced oxidative stress in rats. Nutrients. 2020;12(10):2904. https://doi.org/10.3390/nu12102904

[2] Majeed R, Mahmood AK. Protective effects of ginger ethanolic extract, chitosan nanoparticles, and ginger ethanolic extract-loaded chitosan nanoparticles on pancreatic DNA damage and histological changes in dogs with alloxan-nicotinamide induced type 2 diabetes. Adv Anim Vet Sci. 2024;12(1):32-43. https://doi.org/10.17582/journal.aavs/2024/12.1.32.43

[3] Graziano S, Agrimonti C, Marmiroli N, Gullì M. Utilisation and limitations of pseudocereals (quinoa, amaranth, and buckwheat) in food production: a review. Trends Food Sci Technol. 2022;125:154-65. https://doi.org/10.1016/j.tifs.2022.04.007

[4] Chen Z, Tian R, She Z, Cai J, Li H. Role of oxidative stress in the pathogenesis of nonalcoholic fatty liver disease. Free Radic Biol Med. 2020;152:116-41. https://doi.org/10.1016/j.freeradbiomed.2020.02.025

[5] Bhatti JS, Sehrawat A, Mishra J, Sidhu IS, Navik U, Khullar N, et al. Oxidative stress in the pathophysiology of type 2 diabetes and related complications: current therapeutics strategies and future perspectives. Free Radic Biol Med. 2022;184:114-34. https://doi.org/10.1016/j.freeradbiomed.2022.03.019

[6] Azeem S, Khan U, Liaquat A. The increasing rate of diabetes in Pakistan: a silent killer. Ann Med Surg. 2022;79:103901. https://doi.org/10.1016/j.amsu.2022.103901

[7] Bhutta ZA, Haq ZU, Basit A. Diabetes in Pakistan: addressing the crisis. Lancet Diabetes Endocrinol. 2022;10(5):309-10. https://doi.org/10.1016/S2213-8587(22)00102-4

[8] Adnan M, Aasim M. Prevalence of gestational diabetes mellitus in Pakistan: a systematic review and meta-analysis. BMC Pregn Childbirth. 2024;24:108. https://doi.org/10.1186/s12884-024-06290-9

[9] Shaito A, Thuan DTB, Phu HT, Nguyen THD, Hasan H, Halabi S, et al. Herbal medicine for cardiovascular diseases: efficacy, mechanisms, and safety. Front Pharmacol. 2020;11:422. https://doi.org/10.3389/fphar.2020.00422

[10] Shen N, Wang T, Gan Q, Liu S, Wang L, Jin B. Plant flavonoids: classification, distribution, biosynthesis, and antioxidant activity. Food Chem. 2022;383:132531. https://doi.org/10.1016/j.foodchem.2022.132531

[11] Ciumărnean L, Milaciu MV, Runcan O, Vesa ȘC, Răchișan AL, Negrean V, et al. The effects of flavonoids in cardiovascular diseases. Molecules. 2020;25(18):4320. https://doi.org/10.3390/molecules25184320

[12] Li L, Qin Y, Xin X, Wang S, Liu Z, Feng X. The great potential of flavonoids as candidate drugs for NAFLD. Biomed Pharmacother. 2023;164:114991. https://doi.org/10.1016/j.biopha.2023.114991

[13] Yao YX, Yu YJ, Dai S, Zhang CY, Xue XY, Zhou ML, et al. Kaempferol efficacy in metabolic diseases: molecular mechanisms of action in diabetes mellitus, obesity, non-alcoholic fatty liver disease, steatohepatitis, and atherosclerosis. Biomed Pharmacother. 2024;175:116694. https://doi.org/10.1016/j.biopha.2024.116694

[14] Hosseini A, Razavi BM, Banach M, Hosseinzadeh H. Quercetin and metabolic syndrome: a review. Phytother Res. 2021;35(10):5352-64. https://doi.org/10.1002/ptr.7144

[15] Aleebrahim-Dehkordi E, Soveyzi F, Arian AS, Hamedanchi NF, Hasanpour-Dehkordi A, Rafieian-Kopaei M. Quercetin and its role in reducing the expression of pro-inflammatory cytokines in osteoarthritis. Antiinflamm Antiallergy Agents Med Chem. 2022;21(3):153-65.

[16] Novoselova EG, Lunin SM, Khrenov MO, Glushkova OV, Novoselova TV, Parfenyuk SB. Pancreas β-cells in type 1 and type 2 diabetes: cell death, oxidative stress and immune regulation. Recently appearing changes in diabetes consequences. Cell Physiol Biochem. 2024;58(2):144-55. https://doi.org/10.33594/000000690

[17] Li W, Chen H, Xu B, Wang Y, Zhang C, Cao Y, et al. Research progress on classification, sources and functions of dietary polyphenols for prevention and treatment of chronic diseases. J Future Foods. 2023;3(4):289-305. https://doi.org/10.1016/j.jfutfo.2023.03.001

[18] Adetunji CO, Michael OS, Varma A, Oloke JK, Kadiri O, Akram M, et al. Recent advances in the application of biotechnology for improving the production of secondary metabolites from quinoa. In: Varma A, editor. Biology and biotechnology of quinoa: super grain for food security. Singapore: Springer; 2021. p. 373-96.

[19] Alamri E, Amany B, Bayomy H. Quinoa seeds (Chenopodium quinoa): nutritional value and potential biological effects on hyperglycemic rats. J King Saud Univ Sci. 2022;35(1):102427. https://doi.org/10.1016/j.jksus.2022.102427

[20] Alam S, Sarker MMR, Sultana TN, Chowdhury MNR, Rashid MA, Chaity NI, et al. Antidiabetic phytochemicals from medicinal plants: prospective candidates for new drug discovery and development. Front Endocrinol. 2022;13:800714. https://doi.org/10.3389/fendo.2022.800714
[21] Sharma N, Biswas S, Al-Dayan N, Alhegaili AS, Sarwat M. Antioxidant role of kaempferol in prevention of hepatocellular carcinoma. Antioxidants. 2021;10(9):1419. https://doi.org/10.3390/antiox10091419
[22] Alkandahri MY, Pamungkas BT, Oktoba Z, Shafirany MZ, Sulastri L, Arfania M, et al. Hepatoprotective effect of kaempferol: a review of the dietary sources, bioavailability, mechanisms of action, and safety. Adv Pharmacol Pharm Sci. 2023;2023:1387665. https://doi.org/10.1155/2023/1387665
[23] Casalvara RFA, Ferreira BMR, Gonçalves JE, Yamaguchi NU, Bracht A, Bracht L, et al. Biotechnological, nutritional, and therapeutic applications of quinoa (Chenopodium quinoa Willd.) and its by-products: a review of the past five-year findings. Nutrients. 2024;16(6):840. https://doi.org/10.3390/nu16060840
[24] Ali M, Hassan M, Ansari SA, Alkahtani HM, Al-Rasheed LS, Ansari SA. Quercetin and kaempferol as multi-targeting antidiabetic agents against mouse model of chemically induced type 2 diabetes. Pharmaceuticals. 2024;17(6):757. https://doi.org/10.3390/ph17060757
[25] Mora-Ocación MS, Morillo-Coronado AC, Manjarres-Hernández EH. Extraction and quantification of saponins in quinoa (Chenopodium quinoa Willd.) genotypes from Colombia. Int J Food Sci. 2022;2022:7287487. https://doi.org/10.1155/2022/7287487
[26] Wang T, Wu Q, Zhao T. Preventive effects of kaempferol on high-fat diet-induced obesity complications in C57BL/6 mice. Biomed Res Int. 2020;2020:4532482. https://doi.org/10.1155/2020/4532482
[27] Xu C, Zhang X, Wang Y, Wang Y, Zhou Y, Li F, et al. Dietary kaempferol exerts anti-obesity effects by inducing the browing of white adipocytes via the AMPK/SIRT1/PGC-1α signaling pathway. Curr Res Food Sci. 2024;8:100728. https://doi.org/10.1016/j.crfs.2024.100728
[28] Li J, Zhao Z, Deng Y, Li X, Zhu L, Wang X, et al. Regulatory roles of quercetin in alleviating fructose-induced hepatic steatosis: targeting gut microbiota and inflammatory metabolites. Food Sci Nutr. 2024;13(1):e4612. https://doi.org/10.1002/fsn3.4612
[29] Remigante A, Spinelli S, Straface E, Gambardella L, Caruso D, Falliti G, et al. Antioxidant activity of quercetin in a H2O2-induced oxidative stress model in red blood cells: functional role of Band 3 protein. Int J Mol Sci. 2022;23(19):10991. https://doi.org/10.3390/ijms231910991
[30] Yao W, Fan M, Qian H, Li Y, Wang L. Quinoa polyphenol extract alleviates non-alcoholic fatty liver disease via inhibiting lipid accumulation, inflammation and oxidative stress. Nutrients. 2024;16(14):2276. https://doi.org/10.3390/nu16142276
[31] Zhong L, Lyu W, Lin Z, Lu J, Geng Y, Song L, Zhang H. Quinoa ameliorates hepatic steatosis, oxidative stress, inflammation and regulates the gut microbiota in nonalcoholic fatty liver disease rats. Foods. 2023;12(9):1780. https://doi.org/10.3390/foods12091780
[32] Wang C, Wang X, Song G, Xing H, Yang L, Han K, et al. A high-fructose diet in rats induces systemic iron deficiency and hepatic iron overload by an inflammation mechanism. J Food Biochem. 2021;45:e13578. https://doi.org/10.1111/jfbc.13578
[33] Pasdar Y, Oubari F, Zarif MN, Abbasi M, Pourmahmoudi A, Hosseinikia M. Effects of quercetin supplementation on hematological parameters in non-alcoholic fatty liver disease: a randomized, double-blind, placebo-controlled pilot study. Clin Nutr Res. 2020;9(1):11-19. https://doi.org/10.7762/cnr.2020.9.1.11
[34] Bramlage KS, Bhattacharjee J, Kirby M, Myronovych A, Gupta R, Gonzalez RMS, et al. A diet high in fat and fructose induces early hepatic mitochondrial aging. J Pediatr Gastroenterol Nutr. 2021;73(1):99-102. https://doi.org/10.1097/MPG.0000000000003068
[35] Cui C, Wang C, Han S, Yu D, Zhu L, Jiang P. Impact of a long-term high-fructose diet on systemic metabolic profiles of mice. FASEB Bioadv. 2022;4(8):560-72. https://doi.org/10.1096/fba.2021-00152
[36] Xu Y, Han J, Dong J, Fan X, Cai Y, Li J, et al. Metabolomics characterizes the effects and mechanisms of quercetin in nonalcoholic fatty liver disease development. Int J Mol Sci. 2019;20(5):1220. https://doi.org/10.3390/ijms20051220
[37] Yang H, Li D, Gao G. Kaempferol alleviates hepatic injury in nonalcoholic steatohepatitis (NASH) by suppressing neutrophil-mediated NLRP3-ASC/TMS1-caspase 3 signaling. Molecules. 2024;29(11):2630. https://doi.org/10.3390/molecules29112630
[38] Wang JY, Nie YX, Dong BZ, Cai ZC, Zeng XK, Du L, et al. Quercetin protects islet β-cells from oxidation-induced apoptosis via Sirt3 in T2DM. Iran J Basic Med Sci. 2021;24(5):629-35. https://doi.org/10.22038/ijbms.2021.52005.11792
[39] Dhanya R, Kartha CC. Quercetin improves oxidative stress-induced pancreatic beta cell alterations via mTOR-signaling. Mol Cell Biochem. 2021;476(11):3879-87. https://doi.org/10.1007/s11010-021-04193-3
[40] Mohammadi-Motlagh HR, Sadeghalvad M, Yavari N, Primavera R, Soltani S, Chetty S, et al. β cell and autophagy: what do we know? Biomolecules. 2023;13(4):649. https://doi.org/10.3390/biom13040649
[41] Daraghmeh DN, Karaman R. The redox process in red blood cells: balancing oxidants and antioxidants. Antioxidants. 2024;14(1):36. https://doi.org/10.3390/antiox14010036

Bulletin of
Pharmaceutical & Medicinal Research

Original Article

Cost analysis of malaria prescriptions by prescriber type in healthcare facilities in Lahore

Ismat Shahzadi [a], Sumariah Mehwish [b,*], Jamshaid Akhtar [c], Muhammad Osama Shahid [b]

[a] Medical Stores, PNS RAHAT, Pakistan Navy, Pakistan
[b] Riphah Institute of Healthcare Improvement and Safety, Riphah International Islamic University, Pakistan
[c] Texas Tech University of Health Sciences Center Amarillo Texas, USA
[d] Services Institute of Medical Sciences, Specialized Healthcare & Medical Education Department, Government of Punjab, Pakistan

* Correspondence: sumariah786@gmail.com

Citation: Shahzadi I, Mehwish S, Akhtar J, Shahid MO. Cost analysis of malaria prescriptions by prescriber type in healthcare facilities in Lahore. Bull Pharm Med Res. 2024;3:26-34.

Received: 07 September 2024
Revised: 29 October 2024
Accepted: 07 November 2024
Published: 31 December 2024

Publisher's Note: Logixs Journals remains neutral concerning jurisdictional claims in its published subject matter, including maps and institutional affiliations.

Abstract

Malaria is a significant public health problem in developing countries, including Pakistan, with an annual mortality rate of 50,000 2.6 million cases in 2018. Pakistan continues to be among the top four countries with the highest number of anticipated malaria cases in the region. This descriptive cross-sectional study determined the unit cost of antimalarial prescriptions, compared average treatment costs, and assessed any differences in cost across prescriber types and medication categories. Using purposive sampling, 300 prescriptions of uncomplicated malaria were collected from physicians and consultants practicing at two public tertiary care hospitals in Lahore. The cost of drugs was calculated on the basis of the standard retail price set by the pharmaceutical company. The data were analyzed via SPSS version 25, frequencies were calculated, and two-way ANOVA was performed. The results highlighted that the unit cost of antimalarials prescribed by physicians ranged from Pakistani rupees (PKR) 21-30, whereas the majority of combination therapies for physicians cost up to PKR 50. In comparison, antimalarials prescribed by consultants had unit costs between PKR 31 and 40, with combination therapies falling into either a low-cost band (PKR 1–50) or a higher-cost band (PKR 201–300). Two-way ANOVA revealed a statistically significant interaction between prescriber type and medication category in relation to treatment cost ($p = 0.002$). The study concluded that physicians prescribe lower-cost unit doses and combinations of antimalarial medications than consultants do, and there are significant differences in treatment costs on the basis of prescriber type and the category of medication prescribed. Future research should explore qualitative determinants of prescriber behavior to guide national malaria control and health policy.

Keywords

Malaria treatment cost; Cost-effectiveness analysis; Malaria treatment; Healthcare economics and financing; Prescribing trends; Pharmacy practices

1. Introduction

Malaria is a life-threatening parasitic infection caused by protozoan parasites of the genus Plasmodium and is transmitted through the bite of the female Anopheles mosquito [1]. The five Plasmodium species that infect humans and are primary causative agents of severe malaria include Plasmodium falciparum, Plasmodium vivax, Plasmodium ovale, Plasmodium malariae, Plasmodium knowlesi, and Plasmodium falciparum [2,3]. Fever, nausea, vomiting, headache, joint pain, dizziness, and heartburn are common symptoms of malaria, and factors such as patient history also serve as indicators of malaria [4,5].

The complex life cycle of Plasmodium parasites poses a significant challenge for the development of antimalarial vaccines and resistant drugs [6,7].

Malaria remains a significant public health problem in Pakistan, and 350,000 malaria cases with an estimated 113 deaths were reported in 2021 [8]. In 2022, the World Health Organization (WHO) estimated that 249 million new cases of malaria were diagnosed worldwide, an increase of 5 million cases from the previous year. The countries with a high incidence of malaria included Ethiopia, Nigeria, Uganda, Papua New Guinea, and Pakistan, whereas only Pakistan accounted for approximately 2.1 million new cases. Malaria epidemiology in Pakistan shows fluctuating transmission depending upon regional climate, migration, and health system access, particularly in Punjab and Baluchistan, where cases caused by P. vivax are predominantly other species [9]. However, Pakistan achieved a 40% reduction in malaria incidence from 2015-2020, and it remained among the top four countries with malaria epidemics in the region [10]. Whereas the number of malarial deaths declined from 2015-2019, the incidence rate increased to 10% in 2020 before decreasing slightly in 2022 [8,9,10,11].

According to a study conducted in the United States, the total per-person cost of severe malaria treatment was 2-4 times greater than that of treatment for uncomplicated malaria. The average cost of treatment for hospitalized patients was substantially greater than that for outpatients [United States dollar (USD) 27,642 compared with USD 1,177] [12]. In contrast, patients in Kenya paid USD 15.5 on average for a three-day treatment period for malaria [13]. In Nigeria, indirect costs were greatest in the southern zone, with Nigerian naira (NGN) 13,707.84 and NGN 19,723.55, respectively. For direct costs, the southeast zone had the highest out-of-pocket expenses, NGN 1,391.60, whereas the southern zone had the lowest expenses, NGN 913.08 [14]. Moreover, in 2018, the Rwandan Ministry of Health spent USD 645,647.68 managing malaria in three major geographical zones of the country [15]. In Pakistan, malaria treatment costs are a significant economic burden, accounting for approximately 6.7% of the monthly household income, with low-income populations being extremely affected by out-of-pocket expenses for treatment [16]. This aligns with the WHO, who reported that malaria-endemic countries spend approximately USD 12 billion annually in terms of productivity and healthcare expenditures [17].

In Pakistan, artemisinin-based combination therapies (ACTs) are the WHO-recommended first-line pharmacological agents for uncomplicated P. falciparum and second-line treatments for chloroquine-resistant P. vivax malaria, and chloroquine remains the first-line agent for P. vivax in chloroquine-sensitive cases [18,19,20,21]. However, differences in prescribing behavior among healthcare providers working at different levels and with different capacities in the healthcare system may influence drug selection, dosage, and diagnostic resource utilization. These variations may arise from differences in clinical practice experiences, postgraduate training, adherence to treatment guidelines, and cost awareness in prescribing practices [22,23,24]. It is evident from the scientific literature that prescribers with formal clinical audit experience and proper clinical training in rational drug use demonstrated better adherence to standard treatment guidelines, a lower average prescription cost and better clinical outcomes [25,26].

Despite the high malaria burden in Pakistan, comparative data on prescription costs by prescriber type in urban cities such as Lahore are limited, and existing research focuses on drug efficacy or incidence rather than cost efficiency linked to prescribing behavior [27]. Addressing this gap can guide rational drug use and cost-effective malaria control policies. Therefore, this study aimed to determine the unit cost of antimalarial prescriptions, compare average treatment costs between physicians and consultants, and assess differences in cost across prescriber types and medication categories.

2. Materials and methods

2.1. Study design

A descriptive cross-sectional investigation was carried out over a six-month period, from March to August 2021, in two major public hospitals in Lahore, Pakistan.

2.2. Ethics approval

Ethical clearance was secured from the Ethics Review Committee of Hussain College of Health Sciences, Lahore (reference HCHS/21/ERC/158). Additionally, administrative approval was obtained from the authorities of Shaikh Zayed Medical Complex and Jinnah Hospital prior to study commencement.

2.3. Study setting

Data collection took place at two public tertiary care institutions, Shaikh Zayed Medical Complex and Jinnah Hospital, Lahore [28,29].

2.4. Inclusion and exclusion criteria

Hospital records of outpatients aged 20–40 years who visited the designated healthcare facilities and received a laboratory-confirmed diagnosis of malaria were reviewed by the researcher on the day of the visit. Patients without any other medical conditions, such as allergies, comorbidities or prescription-altering diseases, were included in the study. However, records of patients who revisited the hospital for follow-up or during their malaria incubation period were kept within the exclusion criteria of the study.

2.5. Sample size and sampling technique

The Raosoft sample size calculator was used to determine the required sample size, applying a 95% confidence interval, a 5% margin of error, and a 23.3% pooled malaria prevalence in Pakistan as the response distribution [30]. A sample size of 271 prescriptions was calculated, and a total of 300 prescriptions were acquired from physicians and consultants at the targeted healthcare facilities. A purposive sampling technique was used for the collection of prescriptions and to ensure the inclusion of prescriptions from both prescriber categories.

2.6. Study instrument development

Pakistan's National Malaria Case Management Guidelines and the WHO's prescribing indicators, which are recognized as essential frameworks for evaluating malaria treatment practices, were used as a reference to develop the questionnaire for the study [31,32]. The developed tool was then thoroughly reviewed by relevant experts for its validity, sensitivity and specificity. After approval, the finalized tool was employed for the purpose of data collection.

2.7. Study measures and data collection

The developed instrument collected information about the type of healthcare provider (physician or consultant) and the pharmacological category of prescribed drugs (antimalarials, antibiotics, antipyretics, and other medications). The unit cost of each antimalarial drug was calculated on the basis of the standard retail price of the country as approved by the regulatory body, and the average cost of combination therapy for each prescription was determined by totaling the retail prices of all drugs in that prescription. Data were collected by trained pharmacy graduates by relevant experts under the super-

vision of a senior pharmacist; furthermore, double data entry and independent verification of 10% of the dataset ensured accuracy and internal consistency.

2.8. Statistical analysis

The data were analyzed via the Statistical Package for Social Sciences (IBM Corp., Armonk, NY, USA) version 25.00. Descriptive statistics were calculated for the collected data. Additionally, two-way ANOVA was used to examine the effects of prescriber type, medication category, and their interaction on the cost of malaria treatment. The results were considered statistically significant at $p < 0.05$.

3. Results

Figure 1 presents the distribution of unit costs for antimalarial drugs prescribed by physicians and consultants. Most prescriptions by physicians were priced between PKR 21 and 30, with a substantial proportion also falling within the PKR 1-10 range. Additionally, some physicians prescribed antimalarials that cost less than PKR 1 per unit. In contrast, consultants primarily prescribed antimalarials within the PKR 31-40 range, followed by a smaller number in the below PKR 1 category.

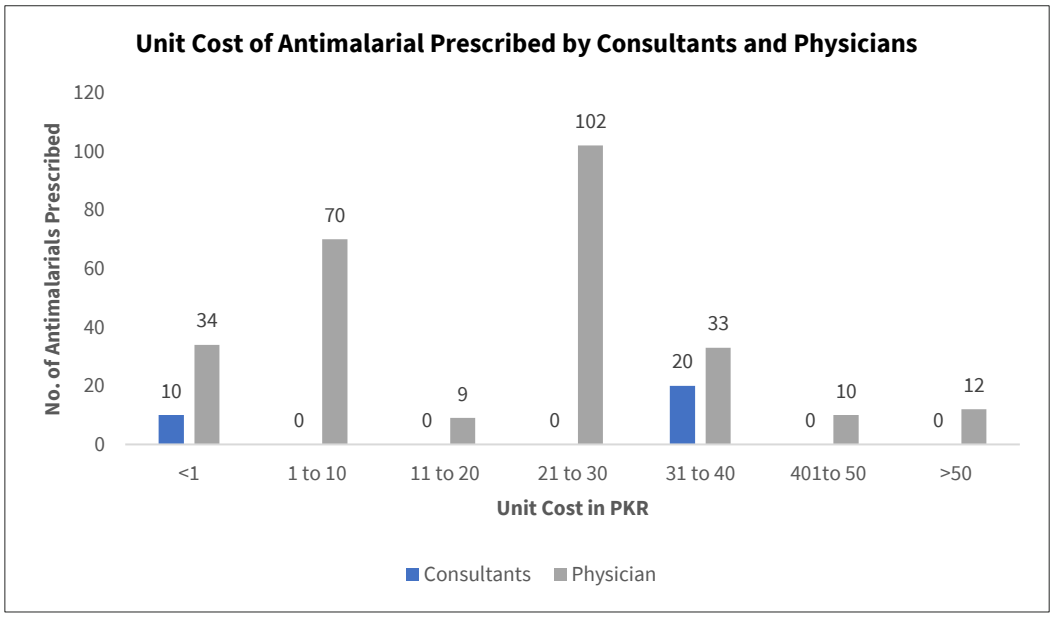


Figure 1. Total cost of antimalarial drugs prescribed by physicians and consultants.

Figure 2 shows the average cost of combination therapies prescribed by physicians and consultants. The majority of prescriptions by physicians were within the PKR 1-100 range, followed by higher-cost categories of above PKR 350 and PKR 201-250. For consultants, the average cost of prescribed combinations was mainly concentrated in two ranges: PKR 1–50 and PKR 201–300.

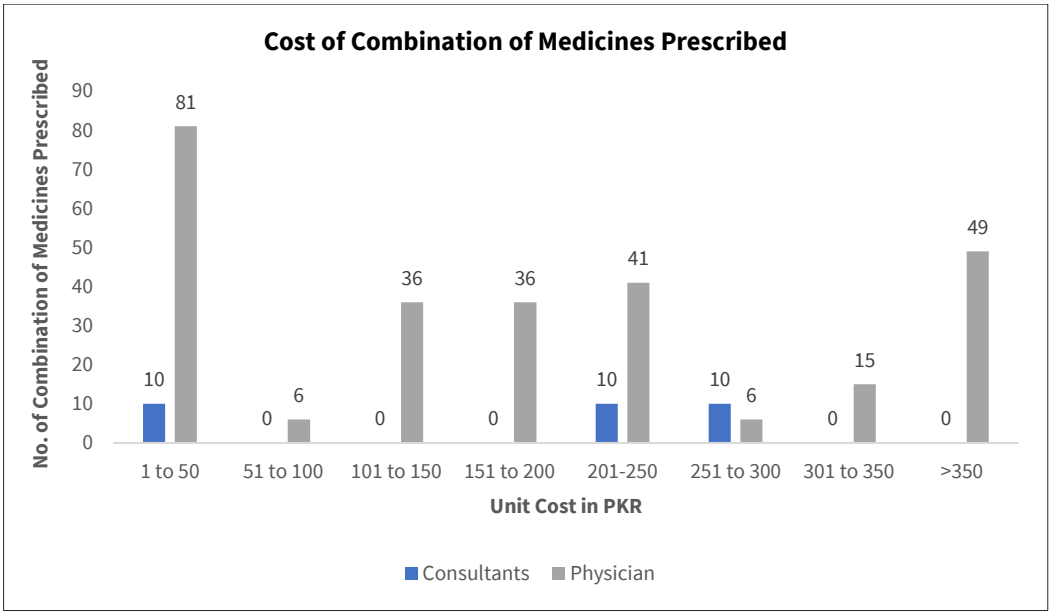


Figure 2. Cost of combination of medicines prescribed by consultants and physicians.

Table 1 presents the results of two-way ANOVA conducted to evaluate whether treatment costs (including antimalarials, antibiotics, and antipyretics) differ by prescriber type and medication category. The interaction effect between prescriber type and medication category was statistically significant ($F = 6.211$, $p = 0.002$), indicating that treatment costs varied depending on both factors. However, the main effect of prescriber type alone was not significant ($p = 0.305$), whereas the medication category had a highly significant effect on treatment cost ($F = 31.270$, $p < 0.001$). The coefficient of determination ($R^2 = 0.139$) indicates that approximately 13.9% of the variance in treatment cost was explained by prescriber type and medication category and suggests that other unmeasured factors, such as disease severity, diagnostic investigations, prescription duration, or institutional procurement policies, may also influence cost outcomes, along with the prescriber type and medication category.

Table 1. Variation in malaria treatment costs by prescriber type and medication category.

Variables	df	F	Sig.
Prescriber	1	1.054	0.305
Medicines	2	31.270	< 0.001 ***
Prescriber * Medicines	2	6.211	0.002 ***

* R squared = 0.139 (adjusted R squared = 0.134); ** Dependent variable: cost per treatment; *** Statistical significance set at $p < 0.05$.

4. Discussion

The study revealed that physicians more frequently prescribed drugs with lower unit costs, less than PKR 30, and, in most cases, fewer than PKR 10. In contrast, consultants more commonly prescribe antimalarials within higher cost ranges, between PKR 31 and PKR 40. The average cost of prescriptions of the combination therapies of the physicians was observed to be in the lower cost range of PKR 1 to PKR 100, with a few extending beyond PKR 350. In contrast, consultants tend to prescribe combinations within the mid-range cost categories, between PKR 201 and PKR 300. Furthermore, malaria treatment cost trends and patterns vary by healthcare professional type and are influenced by the category of medication prescribed.

The results of the current study are in line with those of another study that revealed that the overall treatment cost of malaria is USD 9.31 per person per year [33]. Another study conducted in Kenya reported that the direct medical cost of malaria treatment was USD 7.1 [15]. A study in Nigeria reported that the cost of malaria treatment ranges from USD 2.5-4.1 [34]. However, another Nigerian study reported the direct medical cost of malaria treatment to be USD 5.8 [24]. Moreover, another African study revealed a higher prescription cost for uncomplicated malaria treatment and stated that antimalarial drugs account for 62% of the treatment cost [14,35]. Furthermore, a study from Uganda highlighted the greater cost of malaria treatment for admitted patients than malaria treatment received in facilities other than hospitals [33]. Additionally, studies from African settings suggest that the cost of uncomplicated malaria treatment among pregnant women is relatively high and poses an economic burden [36].

Consultants' higher-cost prescribing may stem from managing more complex or treatment-resistant cases, prompting the use of newer or broader-spectrum antimalarials perceived as more effective or better tolerated. Differences in training, clinical autonomy, and patient socioeconomic status may also influence preferences for branded or combination therapies [37,38]. Systemic factors, including pharmaceutical marketing, limited pharmacoeconomic training, and variable adherence to guidelines, further contribute to differences in the cost of prescriptions [39,40]. In malaria-endemic countries, uncertainty in the results of diagnostic tests may also be a driver of broader empirical prescribing by healthcare professionals [41].

The findings of this study contrast with previous scientific Pakistani literature on malaria treatment prescribing trends, which reported a greater number of drugs per prescription and extensive polypharmacy in prescriptions, ultimately impacting the direct medical cost of treatment [42,43]. One major reason for these high direct medical costs of malaria treatment is the irrational overuse and overprescription of drugs by healthcare professionals in hospital settings [44]. The use of antibiotics to treat uncomplicated malaria contributes to increased treatment costs [45,46]. Furthermore, the choice between treating malaria with a single recommended agent or with multiple agents also influences treatment costs [47]. The practice of healthcare professionals prescribing branded drugs instead of generic equivalents also contributes to rising prescription costs [48].

The present study provides a comparison of malaria treatment costs by calculating the unit dose cost of antimalarial therapy and the total cost per prescription (combined therapy). The study also compared physicians' and consultants' direct medical costs per unit dose of antimalarial agent and per full treatment, establishing an association between the treatment cost and the prescriber type. However, the study did not consider qualitative factors related to healthcare providers (such as the rationale for drug selection), which remains a weakness of the study. Additionally, the sample was limited to outpatients aged 20–40 years at two public hospitals in Lahore, which may limit the generalizability of the findings to other populations and healthcare settings.

5. Conclusions

The study findings confirm that physicians tend to prescribe lower-cost unit doses and combinations of antimalarial medications than consultants do. Moreover, significant differences in treatment costs were observed based on prescriber type, particularly in relation to the category of prescribed medication. These findings highlight the need to promote rational prescribing practices and cost perceptions among healthcare providers operating at different levels of the healthcare system to ensure effective yet cost-efficient malaria treatment. Future studies should qualitatively explore the behavioral and institutional factors driving prescriber choices to better inform policy and practice.

Author contributions: Conceptualization, IS, SM, JA and MOS; methodology, IS, SM, and JA; software, IS, and SM; validation, IS, SM, JA and MOS; formal analysis, IS, SM, and JA; investigation, IS, SM, JA and MOS; resources, IS, SM, and MOS; data curation, IS, SM, JA and MOS; writing—original draft preparation, IS, SM, JA and MOS; writing—review and editing, IS, SM, and JA; visualization, IS, SM, JA and MOS; supervision, IS, SM, and MOS; project administration, IS, SM, and MOS. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no specific grant from the public, commercial, or not-for-profit funding agencies.

Ethics statement: This study obtained ethics approval from the Ethics Review Committee of the Hussain College of Health Sciences, Lahore (No. HCHS/21/ERC/158).

Consent to participate: Not Applicable.

Data availability: The data supporting this study's findings are available from the corresponding author, Sumariah Mehwish, upon reasonable request.

Acknowledgments: None.

Conflicts of interest: The authors declare no conflicts of interest.

References

[1] Phillips MA, Burrows JN, Manyando C, van Huijsduijnen RH, Van Voorhis WC, Wells TNC. Malaria. Nat Rev Dis Primers. 2017; 3:17050. https://doi.org/10.1038/nrdp.2017.50

[2] Walker IS, Rogerson SJ. Pathogenicity and virulence of malaria: sticky problems and tricky solutions. Virulence. 2023;14(1):215 0456. https://doi.org/10.1080/21505594.2022.2150456

[3] Fatmaningsih L, Samasta NA, Octa L. Differences in the life cycle and growth of Plasmodium knowlesi, inui, vivax, malariae, falciparum, ovale. J Biomed Techno Nanomaterials. 2024;1(2):59-69.

[4] Bria YP, Yeh CH, Bedingfield S. Significant symptoms and nonsymptom-related factors for malaria diagnosis in endemic regions of Indonesia. Int J Infect Dis. 2021;103:194-200. https://doi.org/10.1016/j.ijid.2020.11.177

[5] Varo R, Chaccour C, Bassat Q. Update on malaria. Med Clin. 2020;155(9):395-402. https://doi.org/10.1016/j.medcli.2020.05.010

[6] Fikadu M, Ashenafi E. Malaria: an overview. Infect Drug Resist. 2023;16:3339-47. https://doi.org/10.2147/idr.s405668

[7] Popovici J, Ménard D. Challenges in antimalarial drug treatment for vivax malaria control. Trends Mol Med. 2015;21(12):776-88. https://doi.org/10.1016/j.molmed.2015.10.004

[8] Arshad T, Wajahat A, Jabeen A, Ali SH. Malaria and dengue outbreaks during a national disaster in Pakistan: a rising concern for public health. J Glob Health. 2022;12:02076. https://doi.org/10.7189/jogh.12.03076

[9] World Health Organization. World malaria report 2023. 2024 [Cited 17 September 2024]. Available from: https://www.who.int/teams/global-malaria-programme/reports/world-malaria-report-2023.

[10] Al-Awadhi M, Ahmad S, Iqbal J. Current status and the epidemiology of malaria in the Middle East region and beyond. Microorganisms. 2021;9(2):338. https://doi.org/10.3390/microorganisms9020338

[11] González-Sanz M, Berzosa P, Norman FF. Updates on malaria epidemiology and prevention strategies. Curr Infect Dis Rep. 2023;25:131-9. https://doi.org/10.1007/s11908-023-00826-1

[12] Park J, Joo H, Maskery BA, Alpern JD, Weinberg M, Stauffer WM. Costs of malaria treatment in the United States. J Travel Med. 2023;30(3):taad013. https://doi.org/10.1093/jtm/taad013

[13] Watts C, Atieli H, Alacapa J, Lee MC, Zhou G, Githeko A, et al. Rethinking the economic costs of hospitalization for malaria: accounting for the comorbidities of malaria patients in western Kenya. Malar J. 2021;20:429. https://doi.org/10.1186/s12936-021-03958-x

[14] Adesope AA, Yusuf WA, Fawole OO, Yusuf AS. Financial burden of households on the treatment of malaria in Southern Nigeria. NIU J Social Sci. 2023;9(2):111-18. https://doi.org/10.58709/niujss.v9i2.1631

[15] Masimbi O, Schurer JM, Rafferty E, Ndahimana JDA, Amuguni JH. A cost analysis of the diagnosis and treatment of malaria at public health facilities and communities in three districts in Rwanda. Malar J. 2022;21:150. https://doi.org/10.1186/s12936-022-04158-x

[16] Khan M, Mahmood HZ, Noureen S, Muhmood K, Husnain MIU, Hameed Khaliq I. The health burden of malaria and household choices regarding treatment and prevention in Pakistan. Trop Biomed. 2019;36(3):664-76.

[17] World Health Organization. The economic costs of malaria. 2024 [cited 17 September 2024]. Available from: https://www.who.int/teams/global-malaria-programme/reports/economic-costs.

[18] Tripathi H, Bhalerao P, Singh S, Arya H, Alotaibi BS, Rashid S, et al. Malaria therapeutics: are we close enough? Parasites Vectors. 2023;16:130. https://doi.org/10.1186/s13071-023-05755-8

[19] World Health Organization. Malaria. 2024 [cited 17 September 2024]. Available from: https://www.who.int/news-room/questions-and-answers/item/malaria?gad_source=1&gclid=Cj0KCQjwo8S3BhDeARIsAFRmkOPwlxyJkfhB2jW1GSx9bqOuBE539d6YYgUEjEzkaAMRK-IIo4-7vE0aAqWrEALw_wcB.

[20] Hayder H, Uzair M, Ahmad S, Ashraf U, Huzaifa A, Mehmood MS, et al. Strategies for malaria prevention and control. In: Aguilar-Marcelino L, Younus M, Khan A, Saeed NM, Abbas RZ, editors. One Health Triad. Vol. 3. Faisalabad (PK): Unique Scientific Publishers; 2023. p. 157-63.
[21] Ali NS. Evaluation and management of malaria in general practice. J Pak Med Assoc. 1999;49(4):103-5.
[22] Helfrich AM, Fraser JA, Hickey PW. Destination based errors in chloroquine malaria chemoprophylaxis vary based on provider specialty and credentials. Travel Med Infect Dis. 2022;47:102310. https://doi.org/10.1016/j.tmaid.2022.102310
[23] Niyonkuru AE, McLaughlin E, Heath G, Inamuco S, Topazian H, Davis M. Healthcare professional preferences for prescribing artemisinins and quinine for malaria in Burundi. East Afr Health Res J. 2021;5(2):174-81. https://doi.org/10.24248/eahrj.v5i2.670
[24] Conteh L, Shuford K, Agboraw E, Kont M, Kolaczinski J, Patouillard E. Costs and cost-effectiveness of malaria control interventions: a systematic literature review. Value Health. 2021;24(8):1213-22. https://doi.org/10.1016/j.jval.2021.01.013
[25] Atal S, Jhaj R, Mathur A, Rai N, Misra S, Sadasivam B. Outpatient prescribing trends, rational use of medicine and impact of prescription audit with feedback at a tertiary care centre in India. Int J Health Plann Mgmt. 2021;36(3):738-53. https://doi.org/10.1002/hpm.3116
[26] El-Dahiyat F, Salah D, Alomari M, Elrefae A, Jairoun AA. Antibiotic prescribing patterns for outpatient pediatrics at a private hospital in Abu Dhabi: a clinical audit study. Antibiotics. 2022;11(12):1676. https://doi.org/10.3390/antibiotics11121676
[27] Ghaffar MY, Mazhar B, Niaz M, Naeem T, Tabassam M, Abbas M, et al. Prescribing trends and drug-related problems at a tertiary healthcare facility: a descriptive cross-sectional study from Pakistan. J Popul Ther Clin Pharmacol. 2024;31(11):278-91. https://doi.org/10.53555/c9551536
[28] Shaikh Zayed Medical Complex Lahore. Home 2024 [cited 17 September 2024]. Available from: https://szmc.org.pk/Default.aspx.
[29] Jinnah Hospital, Lahore. Home 2024 [cited 17 September 2024]. Available from: https://aimc.edu.pk/jinnah-hospital-lahore/.
[30] Khan MI, Qureshi H, Bae SJ, Khattak AA, Anwar MS, Ahmad S, et al. Malaria prevalence in Pakistan: a systematic review and meta-analysis (2006-2021). Heliyon. 2023;9(4):e15373. https://doi.org/10.1016/j.heliyon.2023.e15373
[31] Atif M, Azeem M, Sarwar MR, Shahid S, Javaid S, Ikram H, et al. WHO/INRUD prescribing indicators and prescribing trends of antibiotics in the Accident and Emergency Department of Bahawal Victoria Hospital, Pakistan. SpringerPlus. 2016;5:1928. https://doi.org/10.1186/s40064-016-3615-1
[32] Ministry of National Health Services Regulation and Coordination. National Malaria Case Management Guidelines. 2024 [cited 17 September 2024]. Available from: https://phkh.nhsrc.pk/sites/default/files/2020-10/Guidelines%20for%20National%20Malaria%20Case%20Management%20Pakistan.pdf.
[33] Batura N, Kasteng F, Condoane J, Bagorogosa B, Castel-Branco AC, Kertho E, et al. Costs of treating childhood malaria, diarrhoea and pneumonia in rural Mozambique and Uganda. Malar J. 2022;21:239. https://doi.org/10.1186/s12936-022-04254-y
[34] Ayogu EE, Mosanya AU, Onuh JC, Adibe MO, Ubaka CM, Ukwe CV. Direct medical cost of treatment of uncomplicated malaria after the adoption of artemisinin-based combination therapy in Nigeria. J Appl Pharm Sci. 2021;11(9):29–34. https://doi.org/10.7324/JAPS.2021.110904
[35] Aryeetey GC, Nonvignon J, Malm K, Owusu R, Baabu BS, Peprah NY, et al. Cost of inappropriate prescriptions for uncomplicated malaria in Ghana. Malar J. 2023;22:157. https://doi.org/10.1186/s12936-023-04581-8
[36] Cirera L, Sacoor C, Meremikwu M, Ranaivo L, Manun'Ebo MF, Arikpo D, et al. The economic costs of malaria in pregnancy: evidence from four sub-Saharan countries. Gates Open Res. 2023;7:47. https://doi.org/10.12688/gatesopenres.14375.2
[37] Das J, Hammer J, Leonard K. The quality of medical advice in low-income countries. J Econ Perspect. 2008;22(2):93–114. https://doi.org/10.1257/jep.22.2.93
[38] Nguyen TA, Knight R, Roughead EE, Brooks G, Mant A. Policy options for pharmaceutical pricing and purchasing: issues for low- and middle-income countries. Health Policy Plan. 2015;30(2):267–80. https://doi.org/10.1093/heapol/czt105
[39] Ofori-Asenso R, Brhlikova P, Pollock AM. Prescribing indicators at primary health care centers within the WHO African region: a systematic analysis (1995–2015). BMC Public Health. 2016;16:724. https://doi.org/10.1186/s12889-016-3428-8
[40] Godman B, Fadare J, Kibuule D, Irawati L, Mubita M, Ogunleye O, et al. Initiatives across countries to reduce antibiotic utilisation and resistance patterns: impact and implications. In: Arora G, Sajid A, Kalia V, editors. Drug resistance in bacteria, fungi, malaria, and cancer. Cham: Springer International Publishing; 2017. p. 539–76.
[41] World Health Organization. Guidelines for the treatment of malaria.Third edition. 2024 [17 September 2024]. Available from: https://www.afro.who.int/publications/guidelines-treatment-malaria-third-edition
[42] Asghar MA, Mumtaz N, Asghar MA, Niaz S, Zaheer K, Raza ML. Prescribing behaviour of practitioners in public and private hospitals in Pakistan evaluated using the World Health Organization (WHO) indicators: a comparative approach. Pharm Hosp Clin. 2017;52(3):299–305. https://doi.org/10.1016/j.phclin.2017.06.002
[43] Qamariat H. Rational and irrational drug use: factors, impacts and strategies to combat irrational drug use: a narrative review. Int J Pharm Sci Clin Pharm. 2021;2(1):6–17.
[44] Otambo WO, Olumeh JO, Ochwedo KO, Magomere EO, Debrah I, Ouma C, et al. Health care provider practices in diagnosis and treatment of malaria in rural communities in Kisumu County, Kenya. Malar J. 2022;21:129. https://doi.org/10.1186/s12936-022-04156-z
[45] Anjorin ET, Olulaja ON, Osoba ME, Oyadiran OT, Ogunsanya AO, Akinade ON, et al. Overtreatment of malaria in the Nigerian healthcare setting: prescription practice, rationale and consequences. Pan Afr Med J. 2023;45:111. https://doi.org/10.11604/pamj.2023.45.111.31780

[46] van Dorst PWM, van der Pol S, Olliaro P, Dittrich S, Nkeramahame J, Postma MJ, et al. Cost-effectiveness of test-and-treat strategies to reduce the antibiotic prescription rate for acute febrile illness in primary healthcare clinics in Africa. Appl Health Econ Health Policy. 2024;22:701–715. https://doi.org/10.1007/s40258-024-00889-x

[47] Zaman N, Haq FU, Khan Z, Uallah W, Ualiyeva D, Waheed Y, et al. Incidence of malarial infection and response to antimalarial drugs at Districts Lower Dir and Swat of Khyber Pakhtunkhwa, Pakistan. Dialogues Health. 2022;1:100035. https://doi.org/10.1016/j.dialog.2022.100035

[48] Sajid N, Aziz A, Asif S, Ashraf S, Iqbal AA, Ali G, et al. Evaluation of cost-effective therapy by comparing brands of the same formulation in Pakistan. Curr Pharm Res. 2024;2(1):90–111. https://doi.org/10.32350/cpr.21.05

Bulletin of
Pharmaceutical & Medicinal Research

Original Article

Assessment of academic performance, preparedness, and career orientation among Doctor of Pharmacy students: a cross-sectional study from Sargodha, Pakistan

Safa Noor [a], Jawaria Jabeen [a], Waseem Kashif [b], Nabeel Ahmed [a,c,*]

[a] College of Pharmacy, University of Sargodha, Pakistan
[b] Ullevål Hospital, Oslo, Norway
[c] School of Pharmacy, Kunming Medical University, Kunming, China

* Correspondence: nabeelahmed141947@gmail.com

Citation: Noor S, Jabeen J, Kashif W, Ahmed N. Assessment of academic performance, preparedness, and career orientation among Doctor of Pharmacy students: a cross-sectional study from Sargodha, Pakistan. Bull Pharm Med Res. 2024;3:35-48.

Received: 11 August 2024
Revised: 14 November 2024
Accepted: 29 November 2024
Published: 31 December 2024

Publisher's Note: Logixs Journals remains neutral concerning jurisdictional claims in its published subject matter, including maps and institutional affiliations.

Abstract

Pharmacy students face critical decisions about their career paths as they approach graduation. However, in Pakistan, data are limited on how academic performance, job preparedness, and career orientation are interrelated among pharmacy undergraduates. This study aimed to assess academic performance, job-seeking preparedness, and career orientation among fourth- and fifth-year Doctors of Pharmacy (Pharm.D.) students and to evaluate the availability and utilization of institutional career counseling services. A descriptive cross-sectional study involving 183 fourth- and fifth-year Pharm.D. was conducted at the College of Pharmacy, University of Sargodha. students. Data were collected via a self-structured, expert-validated questionnaire covering academic performance, job preparedness, and career orientation. The data were analyzed via SPSS and RStudio, which employ descriptive statistics, independent samples t tests, and Pearson correlation analysis. Most participants were female (65.57%), urban residents (72.68%), and unmarried (95.08%), with 69.95% having one to three siblings with a university education. A CGPA ≥ 3.5 was reported by 60.66% of the students, whereas only 20.77% had research experience. Workshop and conference participation was high (85.25% and 83.06%, respectively), but institutional support was limited—only 19.67% received help from the student affairs department, and 29.51% received guidance from a student society or organization. Although 89.62% could make a CV and 71.58% could independently apply for jobs, only 46.45% could write a cover letter, and 42.08% felt prepared for interviews. The awareness of private-sector pharmaceutical roles (15.85%) exceeded that of public-sector roles (13.11%), and the knowledge of community (70.49%) and clinical (64.48%) pharmacies was greater than that of industrial (8.20%) or hospital (38.25%) positions. Career orientation toward nonpharmaceutical sectors was relatively stronger in the public (49.73%) and private (45.90%) domains. Gender ($p = 0.030$) and year of study ($p = 0.047$) were significantly associated with preparedness, favoring male and 5th-year students. A moderate correlation existed between academic performance and preparedness ($r = 0.38$), whereas correlations between academic performance and career orientation ($r = –0.02$) and between preparedness and career orientation ($r = 0.09$) were weak or negligible. Pharmacy undergraduates in their fourth and fifth professional years were academically sound but demonstrated deficiencies in job-seeking readiness and awareness of nontraditional career paths. However, exposure of students to career counseling by institutions has remained limited; findings highlight the need for career guidance services in a structured manner, intense research engagement, and vast exposure of students as well as fresh graduates to diverse professional pathways beyond traditional pharmacy roles.

Keywords

Pharmacy profession, pharmaceutical career counseling, career orientation, career preparedness, undergraduate pharmacy students, fresh graduates, pharmacy education

1. Introduction

Pharmacy has more than 3.7 million professionals worldwide, and it is regarded as the third largest healthcare profession, highlighting its essential role in patient care and healthcare systems [1]. The traditional role of pharmacists has evolved from the manufacturing, compounding and dispensing of drugs to a broader range of responsibilities, including clinical services, research and management in the healthcare system. Pharmacists, as professionals of the contemporary world, are essential members of health teams and are recognized for their valuable technical inputs and contributions across various domains of the healthcare system [2]. The diverse nature of the pharmacy profession offers pharmacists a wide range of careers in the pharmaceutical sector, including but not limited to pharmaceutical manufacturing, quality control, sales, marketing, research and development, pharmacoeconomics, and pharmacovigilance, as well as associations with regulatory bodies such as the Drug Regulatory Authority of Pakistan (DRAP) in different professional roles. Furthermore, hospital pharmacists play clinical roles in patient care and are involved in areas such as aseptic dispensing, extemporaneous compounding, sterile preparations, topical preparations and pharmacovigilance [3,4].

In Pakistan, pharmacy education evolved with the introduction of the Pharmacy Act of 1967, which constituted the first formal three-year baccalaureate degree program, which was then extended to a four-year degree program from 1978-1979. The curriculum was further enhanced to include a five-year Doctor of Pharmacy (Pharm.D.) degree from 2003–2004, which included clinical pharmacy as its major course [5]. According to 2023 data from the Pharmacy Council of Pakistan (PCP), 14,405 Pharm.D. students were expected to graduate from 153 public and private institutions across the country [6]. Furthermore, the number of registered pharmacists in Pakistan, i.e., 33,455 recorded five years ago, has also been steadily increasing every year [7]. Given the growing number of professionals in the field, the future of pharmacy services and careers in Pakistan is poised for significant developments in the profession.

Career orientation and preparedness are fundamental in directing career-related decisions and fostering effective self-management behavior among graduates [8]. Career orientation is regarded as an individual's preference for specific career opportunities and pathways in professional development [9]. Preparedness refers to the usual job readiness skills of an individual, such as writing resumes, interview preparation, and basic job application capabilities. In general, career orientation is referred to as the level of awareness and preferences of a graduate regarding specific sectors or professional roles within pharmaceutical sciences and related industries [10]. The choices made regarding academic disciplines and career paths are important in aligning personal interests and motivations with professional goals. Effectively managing career goals in early adulthood can lead to greater professional development and career satisfaction in the future [11]. Therefore, evaluating pharmacy students' awareness of different sectors of the pharmaceutical sciences is vital for informed career planning and decision making.

Pharmacists are increasingly venturing into diverse career paths across the healthcare system, including professional roles such as disease counselors (e.g., diabetes educators), officers in healthcare supply chain management, health insurance companies, and clinical trial associates, as well as other important professional positions across both the public and private sectors. Furthermore, the scope of hospital pharmacy practice has expanded from traditional warehousing and inventory management to specialized areas in clinical pharmacy, e.g., infectious disease control and oncology pharmacotherapy, and pharmacists now also play critical roles in drug information centers

within hospitals. International scientific literature regarding pharmacy students' preferences for specific careers in Bachelor of Pharmacy and Pharm.D. programs and highlights various career paths, such as hospital pharmacy, community pharmacy, clinical pharmacy, industry, and academia, as the preferred choices among pharmacy students [4,12,13,14,15].

However, few studies have specifically evaluated the associations among academic performance, preparedness, and career orientation among pharmacy students and graduates, particularly in terms of job-seeking skills and sector-specific career awareness. This gap is particularly important in developing countries such as Pakistan, where students and graduates face limited institutional support and are limited to nonexposure to broader horizons of pharmacy careers and pathways [16,17]. Addressing these gaps is important for strengthening career guidance programs and supporting the professional development of students as well as fresh graduates across the country. Therefore, this study aimed to assess academic performance, job-seeking preparedness, and career orientation among fourth- and fifth-year professionals, Pharm.D. students and to evaluate the availability and employment of institutional career counseling services.

2. Methodology

2.1. Study design

The study utilized a cross-sectional design and was conducted for three months, from May 2023 to July 2023.

2.2. Study setting

The study was conducted at the College of Pharmacy, University of Sargodha, a major public sector university in Punjab, Pakistan, established in 2002. The University has approximately 19,000 students in 22 departments and four constituent colleges. The College of Pharmacy has more than 600 students enrolled in undergraduate (Pharm.D.) and postgraduate programs (M. Phil. and PhD). The college is unique in Pakistan because it has an industrial unit along with a model pharmacy that provides quality medicines and services to the local community at a cheap price compared with the market [18].

2.3. Ethical approval

Ethical approval for the study was obtained from the ethical review committee of the University of Sargodha (No. SU/REC/1491). Furthermore, permission was obtained from the university administration and the College of Pharmacy for data collection and for conducting the study.

2.4. Participant recruitment

The study included all regularly enrolled Pharm.D. students in their fourth and fifth professional years (8^{th}–10^{th} semesters) at the University of Sargodha who provided consent to participate. However, the study did not include transferred students from other institutions; foreign students enrolled in the Pharm.D. program, or students who had resumed their studies after taking a leave of absence.

2.5. Sample size and sampling technique

The sample size was calculated via the OpenEpi sample size calculator, which maintains a 95% confidence interval and a 5% margin of error [19]. A prevalence of 10.10% was used on the basis of a prior study conducted among pharmacy students in Lahore, which reported that 10.10% of participants were unaware of the scope of the pharmacy

profession [20]. This yielded a minimum required sample of 140 students. To address nonresponders and incomplete questionnaires, the final sample size was increased to 200. The purposive sampling technique was used to target the 4th and 5th professional years students at the University of Sargodha.

2.6. Questionnaire development

The questionnaire was developed through a comprehensive literature review and included the questions most relevant to the objectives of the study and target population [21]. It consists of four major sections: demographics, academic performance, preparedness, and career orientation. The questionnaire was then reviewed by field experts to ensure content validity, and after their feedback was incorporated, the finalized tool was used for data collection.

2.7. Study measures

The sociodemographic section collected data on the age of the participants, sex, marital status, residential status, family income, education level of the siblings, year of study, and presence of a pharmacist in the family.

The academic performance section comprises eight binary (yes/no) items related to the academic profiles of students. These included CGPA, internship experience, research experience, conference participation, workshop participation, attendance at pharmacy career sessions, support from the student affairs department, and guidance from any student society or organization. Each response was marked as ‘0’ or ‘1’, resulting in a cumulative academic score ranging from 0-8; total scores were categorized as poor for scores less than 4, average for scores between 4-6, and good for scores greater than 6.

The preparedness section evaluated the readiness of students for job-seeking operations via ten close-ended questions, addressing their understanding of cover letters, their knowledge of the difference between a curriculum vitae (CV) and a resume, their competence in preparing a professional CV and writing a cover letter, their knowledge of areas to look for jobs, their perceived preparedness for interviews, their confidence in performing well in interviews, their ability to apply for jobs independently, their familiarity with career options for pharmacists, and their understanding of the difference between professional pharmacists and pharmacy technicians. Each item was marked as ‘0’ or ‘1’, with a maximum possible score of 10. Scores were categorized as poor if they were less than 5, average if they were between 5 and 7, and good if they were greater than 7.

The career orientation section measured the level of awareness of students for sector-specific roles within the healthcare profession and related fields across the public and private sectors with the help of eight open-ended questions (S1 to S8). Each response was evaluated and categorized as "yes" for clearly valid and specific answers; "Maybe" for general, vague, or partially correct answers; and "No" for incorrect, irrelevant, or missing responses. For scoring purposes, “Yes” responses were assigned a value of 1, “Maybe” a value of 0.5, and “No” a value of 0. The cumulative score for this section ranged from 0-8 and was categorized as poor for scores less than 4, average for scores between 4 and 6, and good for scores greater than 6.

2.8. Data collection

Data were collected via a self-administered questionnaire distributed to suitable participants for the study during their scheduled academic sessions. Prior to participation, all the respondents were informed about the objectives and scope of the study. Participation in the study was voluntary, and informed written consent was obtained from each

respondent. The questionnaire was completed anonymously to maintain confidentiality and reduce response bias.

2.9. Data analysis

Descriptive statistics were used for sociodemographic variables, academic performance, preparedness, and career orientation. Bivariate analyses were performed to explore associations between sociodemographic predictors (such as gender, residential status, family income, academic year, and the presence of a pharmacist in the family) and outcome variables (academic performance, preparedness, and career orientation). Independent samples t tests were used to compare binary categorical predictors, whereas Pearson's correlation coefficients (r) were computed for ordinal or continuous variables (e.g., family income, siblings' university education). The assumption of normality was verified via Q–Q plots prior to applying parametric tests. Statistical significance was set at $p < 0.05$. Additionally, interrelationships among the three outcome domains were visualized via a Pearson correlation matrix heatmap.

3. Results

3.1. Sociodemographic profile

Table 1 shows the sociodemographic profile of 183 Pharm.D. students out of the 200 questionnaires distributed, yielding a response rate of 91.50%. Most of the students were aged 23 years (35.52%), followed by 22 years (24.59%) and 24 years (23.50%). A total of 65.57% of the sample included female students, whereas 34.43% were male. Most participants resided in urban areas (72.68%), whereas 27.32% reported living in rural areas.

Table 1. Sociodemographic characteristics of the study participants (N = 183).

Variables		Frequency (%)
Age (years)	21	15 (8.20)
	22	45 (24.59)
	23	65 (35.52)
	24	43 (23.50)
	25	14 (7.65)
	26	1 (0.55)
Gender	Male	63 (34.43)
	Female	120 (65.57)
Residential status	Urban	133 (72.68)
	Rural	50 (27.32)
Family income (monthly) in PKR	< 50,000	65 (35.52)
	50,000 – 100,000	79 (43.17)
	> 100,000	39 (21.31)
Marital status	Married	9 (4.92)
	Unmarried	174 (95.08)
Number of siblings with university education	0	33 (18.03)
	1-3	128 (69.95)
	4-6	18 (9.84)
	> 6	4 (2.19)
Year of study	Fourth	99 (54.10)
	Fifth	84 (45.90)
Presence of a pharmacist in the family	No	157 (85.79)
	Yes	26 (14.21)

Table 1 further shows that monthly family income was mostly between PKR 50,000 and 100,000 (43.17%), followed by less than PKR 50,000 (35.52%) and more than PKR 100,000 (21.31%). Most students were unmarried (95.08%). With respect to siblings' educational attainment, 69.95% had 1–3 siblings with a university education, 18.03% had none, 9.84% had 4–6 siblings, and 2.19% had more than six. More than half of the students were in their fourth year (54.10%), and 45.90% were in their fifth year. A total of 14.21% reported having a pharmacist in the family.

3.2. Academic performance, preparedness for job seeking, and career orientation awareness

Among the 183 Pharm.D. students, 60.66% had a CGPA ≥ 3.5, whereas 39.34% had a CGPA below 3.5 (Table 2). Internship experience was reported by 66.67% of the participants, whereas research experience was considerably lower, reported by only 20.77%. A majority of the students attended conferences (83.06%) and workshops (85.25%). Most of the students (60.11%) reported attending pharmacy career sessions. However, only 19.67% reported receiving support from the student affairs department, and 29.51% had received guidance from any society or organization.

Table 2. Categorical distribution of academic performance, preparedness, and career orientation among Pharm.D. students (N = 183).

Variables	Frequency (%)	Frequency (%)	Frequency (%)
	< 3.5, Yes	**≥ 3.5, No**	**Maybe**
Academic Performance			
CGPA	72 (39.34)	111 (60.66)	-
Internship experience	122 (66.67)	61 (33.33)	-
Research experience	38 (20.77)	145 (79.23)	-
Conference experience	152 (83.06)	31 (16.94)	-
Workshop experience	156 (85.25)	27 (14.75)	-
Attended pharmacy career session	110 (60.11)	73 (39.89)	-
Support from the student affairs department	36 (19.67)	147 (80.33)	-
Guidance from any society or organization	54 (29.51)	129 (70.49)	-
Preparedness for Job-Seeking			
Familiar with cover letters	114 (62.30)	69 (37.70)	-
Knows the difference between a CV and a resume	111 (60.66)	72 (39.34)	-
Can make a professional CV	164 (89.62)	19 (10.38)	-
Can write a cover letter	85 (46.45)	98 (53.55)	-
Knows where to look for jobs	108 (59.02)	75 (40.98)	-
Is prepared for an interview	77 (42.08)	106 (57.92)	-
Can perform well in an interview	125 (68.31)	58 (31.69)	-
Can apply for jobs on their own	131 (71.58)	52 (28.42)	-
Familiar with career options for pharmacists	166 (90.71)	17 (9.29)	-
Understands difference between pharmacist and pharmacy technician roles	18 (9.84)	165 (90.16)	-
Career Orientation Awareness			
Pharmaceutical careers in the public sector	24 (13.11)	72 (39.34)	87 (47.54)
Nonpharmaceutical careers in the public sector	91 (49.73)	67 (36.61)	25 (13.66)
Pharmaceutical careers in the private sector	29 (15.85)	20 (10.93)	134 (73.22)
Nonpharmaceutical careers in the private sector	84 (45.90)	58 (31.69)	41 (22.40)
Job designations in industry	15 (8.20)	38 (20.77)	130 (71.04)
Job designations in hospital	70 (38.25)	53 (28.96)	60 (32.79)
Job designations in clinical pharmacy	118 (64.48)	46 (25.14)	19 (10.38)
Job designations in community pharmacy	129 (70.49)	32 (17.49)	22 (12.02)

In terms of preparedness for job seeking, 62.30% were familiar with cover letters, 60.66% understood the difference between a CV and a resume, and 89.62% could make a professional CV. However, only 46.45% were able to write a cover letter. Awareness of job search platforms was present in 59.02% of the students, whereas 42.08% felt prepared for interviews, and 68.31% believed that they could perform well in one. A large majority (71.58%) reported that they could apply for jobs independently. Familiarity with career options for pharmacists was high (90.71%), yet only 9.84% correctly understood the difference between the pharmacist and pharmacy technician roles.

Table 2 further delineates the career orientation awareness among Pharm.D. students; valid awareness (coded as "yes") of pharmaceutical careers in the public sector was present in 13.11% of participants, whereas 49.73% showed such awareness of non-pharmaceutical public sector roles. Awareness of pharmaceutical careers in the private sector was observed in 15.85%, with 45.90% for nonpharmaceutical roles in that domain. Specific knowledge of job designations in industry was identified in only 8.20% of the students. For job designations in hospitals, 38.25% demonstrated valid awareness, whereas higher proportions were observed for clinical pharmacies (64.5%) and community pharmacies (70.49%).

3.3. Categorical distributions of academic performance, preparedness, and career orientation

Figure 1 presents the distribution of cumulative scores across the three domains.

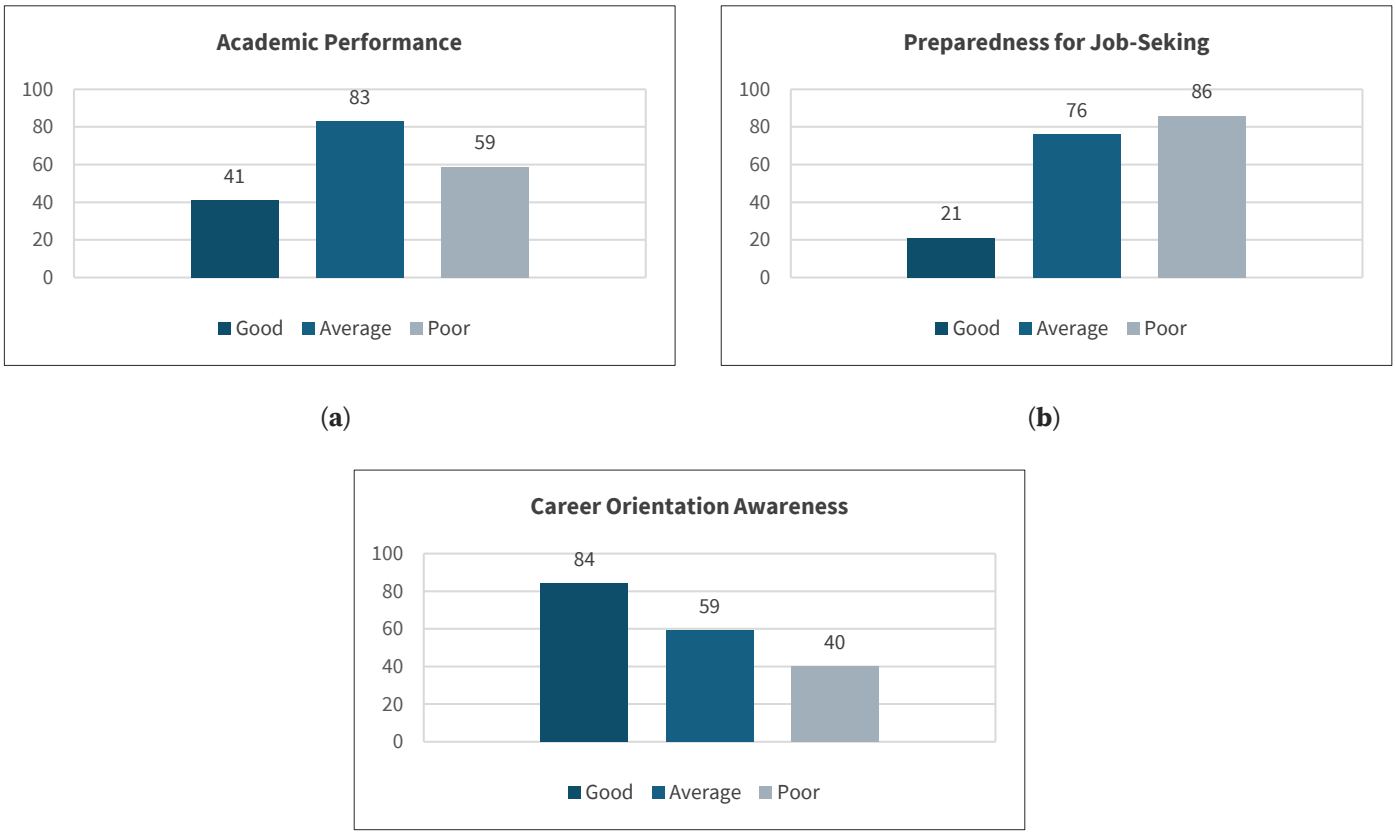


Figure 1. Categorical distribution of cumulative scores among study participants. (a). Academic performance (maximum score = 8; poor < 4, average = 4–6, good > 6); (b). Preparedness for job-seeking (maximum score = 10; poor < 5, average = 5–7, good > 7); (c). Career orientation awareness (maximum score = 8; poor < 4, average = 4–6, good > 6).

In terms of academic performance, 45.40% of the students were classified as average, 32.20% as poor, and 22.40% as good. Preparedness for job seeking was poor for 46.90% of the students, average for 41.50%, and good for 11.50%. In terms of career orientation awareness, 45.90% of the students were in the good category, 32.24% were on average, and 21.86% were poor.

3.4. Associations of sociodemographic variables with academic performance, preparedness, and career orientation

Table 3 presents the results of the bivariate analysis between the sociodemographic characteristics and the three outcome variables. Gender was significantly associated with preparedness for job seeking ($p = 0.030$), with male students reporting greater preparedness. Years of study also showed a significant association with preparedness ($p = 0.047$), where fifth-year students reported higher preparedness levels than fourth-year students did. No significant associations were observed for academic performance or career orientation awareness across any of the sociodemographic variables. Weak positive correlations were noted between preparedness and both family income (r = 0.057) and the number of siblings with a university education (r = 0.141).

Table 3. Bivariate analysis of the associations of sociodemographic characteristics with academic performance, preparedness, and career orientation among Pharm.D. students (N = 183).

Variables	Academic Performance	Preparedness for Job-Seeking	Career Orientation Awareness
Gender	0.445	0.030	0.819
Residential status	0.352	0.171	0.505
Family income	0.506	0.487 (r = 0.057)	0.262 (r = -0.092)
Marital status	0.813	0.141	0.185
Number of siblings with university education	0.450	0.059 (r = 0.141, weak)	0.833 (r = 0.016)
Year of study	0.456	0.047	0.989
Presence of pharmacist in family	0.928	0.695	0.699

[*] Statistical associations were examined via independent samples t tests for binary categorical variables and Pearson's correlation for ordinal/continuous predictors. [**] $p < 0.05$ was considered statistically significant. Pearson's r indicates the strength and direction of correlation (positive or negative).

3.5. Interrelationships among academic performance, preparedness, and career orientation

Figure 2 displays the Pearson correlation coefficients between academic performance, preparedness for job seeking, and career orientation awareness. A moderate positive correlation was observed between academic performance and preparedness (r = 0.38), whereas preparedness and career orientation awareness were weakly positively correlated (r = 0.09). No meaningful correlation was found between academic performance and career orientation awareness (r = –0.02).

Figure 2. Correlation matrix between academic performance, job-seeking preparedness, and career orientation awareness among Pharm.D. students. The color intensity shows the strength of the correlation, with darker shades indicating stronger relationships. The Pearson correlation coefficient (r) indicates the direction of the relationship (positive or negative), with a value of r closer to ±1 signifying a strong linear relationship, whereas values near 0 indicate weak or no linear association.

4. Discussion

The study highlighted that the majority of respondents were female, from urban areas, and single, with many having at least one sibling to be a university graduate. Most students had strong academic performance records but limited exposure to research activities in the pharmaceutical sciences. While a significant proportion of the respondents engaged in professional development opportunities, many of the respondents lacked adequate career guidance and institutional support. Most of the respondents felt confident in basic job-seeking skills, including creating a CV and applying for different positions, yet more than half of the respondents did not feel prepared for job interviews. They had a better level of awareness of pharmaceutical roles, but their knowledge of related or nonpharmaceutical careers was limited. A moderate positive correlation was observed between academic performance and overall job-seeking preparedness; however, academic performance was not significantly associated with sector-specific career orientation. Notably, male respondents and those in the final professional year presented greater self-reported job-seeking skills than female respondents and fourth professional year students did.

The finding that students lack research experience is supported by Ethiopian studies, which highlight the weak capacity of undergraduate pharmacy students for research and that the number of research projects has also declined with time [22]. Similarly, another Ethiopian study highlighted the overall quality of research by pharmacy students

to be average and often confined to a narrow focus with limited study designs [23]. A study performed at Qatar University revealed better significance of research and confidence in conducting research among students; however, most participants lacked data analysis skills [24]. Insufficient research facilities in laboratories, financial aid, experienced mentors, and motivation for research play vital roles in the limited understanding of research among undergraduate pharmacy students [25]. Furthermore, process complexity, limited social interactions, poor communication, depression among students and old curricula also influence undergraduate students' research activities [26].

An Indonesian study supported the findings of the current study and highlighted that many pharmacy students struggled to understand their career orientation and highlighted a lack of effective institutional career guidance to the students [27]. In contrast, an Arabian study highlighted that the institution provided career guidance services but that only a limited number of students reached out to a career counsellor [28]. Another study highlighted the better satisfaction of students with the career development services offered at their institution but recommended networking with alumni, exposure to different pharmacy careers and a potential focus on the job searching process [29]. However, not all student populations are equally uninformed. For example, one study reported that pharmacy students in another setting had a relatively good understanding of career options in the pharmaceutical and healthcare sectors, suggesting that access to information and guidance may differ by institution or region [30]. Overall, career decision-making is multifaceted: opportunities for growth, self-esteem and self-efficacy, family and peer influence, psychological factors, the presence of a family business, and gender have all been identified as important determinants of pharmacy students' career choices [31,32,33,34,35].

With respect to job readiness, the results of the current study are supported by a Saudi study highlighting better job readiness among pharmacy students and fresh graduates, with many focusing on professional roles in pharmaceutical marketing [36]. However, a study on pharmacy interns reported that workplace supervisors reported deficiencies in the communication skills and level of confidence of the interns [37]. Similarly, an Australian study highlighted that an excessive academic workload and a limited understanding of the healthcare system can limit the work readiness of new healthcare graduates [38]. Moreover, personal characteristics such as social intelligence, practical competence, and organizational acumen have been associated with contributing significantly to the job readiness of a fresh graduate [39,40].

In terms of career orientation, our results are in line with those of previous studies that highlighted that Pharm.D. Students tend to focus on traditional professional pharmacy roles. A study revealed that a majority of final professional-year pharmacy students were interested in clinical pharmacy, pharmaceutical manufacturing and quality control [41]. Similarly, an Arabian study highlighted the preference of pharmacy students for careers in hospital and community pharmacy settings; similarly, another study highlighted considerable interest among pharmacy students in working in research institutes, pharmaceutical companies, or hospitals [42,43]. In Pakistan, a comparable trend is observed among undergraduate pharmacies and traditional roles in hospitals or community pharmacies, followed by academic positions and professional roles in the pharmaceutical industry [44]. This inclination toward the traditional position is predictable, as the pharmacy curriculum itself emphasizes core practice areas and thus naturally channels students toward those professional pathways [45]. Additionally, external factors, such as the desire to serve in the public sector, salary expectations, preferred working hours, the work environment and geographic location, expected career growth, and even demo-

graphic factors, including gender, can significantly influence the career preferences of pharmacy students [46,47].

The comprehensive scope and context specificity are among the major strengths of this study, with a potential focus on assessing academic performance, job preparedness, and sector-specific career awareness among pharmacy students. However, the sample was drawn from a single public-sector university, which may limit the generalizability of the findings of the current study to other institutions. The cross-sectional design depicts perceptions at one point in time and cannot establish causality or account for changes as students' progress into their professional careers. The study also did not include qualitative methods to explore insight into the causal reasons or thought processes behind many of the observed trends. Furthermore, the study focused only on students in their fourth and final professional years for job preparedness and intentions to pursue specific careers in pharmaceuticals but did not pursue actual career outcomes after graduation, an area that future research could explore.

The study recommends incorporating qualitative research in the same area to better understand the personal motivations, concerns, and decision-making processes of pharmacy students for career choices. Universities offering graduate degree programs in pharmaceutical sciences should strengthen the career preparation of students by establishing career counseling services and proactively encouraging the participation of students. Faculties may be made part of career-focused seminars and workshops so that students can develop a better understanding of pharmaceutical careers and related competencies for career planning and securing positions successfully in organizations. Students should also be exposed to a wider array of pharmaceutical careers and pathways through alumni networking events, mentorship programs with professionals from multiple pharmaceutical sectors, and career fairs that also include nontraditional pharmaceutical roles and opportunities for graduates. The provision of research opportunities to undergraduate pharmacy students as well as internships in both clinical and industrial settings can further enhance their practical skills and confidence. By implementing such changes, pharmacy institutions and regulatory bodies can better prepare fresh pharmacy graduates not only to excel academically but also to successfully steer diverse pharmaceutical career opportunities.

5. Conclusions

Pharmacy undergraduate students demonstrated a moderate level of academic performance and a reasonable level of awareness of traditional pharmaceutical career pathways; however, notable gaps exist in their understanding of nontraditional roles and in overall job readiness. The findings highlight that academic performance does not translate into sector-specific career orientation or practical job-seeking expertise among pharmacy students. Specifically, limited research exposure, low interview preparedness, and insufficient career guidance underline critical gaps in current pharmacy degree programs from the point of view of the pharmaceutical career. This study highlights the urgent need to introduce career counseling programs, capacity-building workshops, and exposure to diverse career pathways to ensure that fresh pharmacy graduates are well trained to traverse into an evolving competitive job market.

Author contributions: Conceptualization, SN, JJ, WK and NA; methodology, SN, JJ, WK and NA; software, WK and NA; validation, NA; formal analysis, SN, JJ, and NA; investigation, SN, JJ, WK and NA; resources, JJ, and NA; data curation, SN, JJ, and NA; writing—original draft preparation, SN, JJ, and NA; writing—review and editing, WK and NA; visualization, NA; supervision, SN, JJ, and NA; project administration, NA. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no specific grant from the public, commercial, or not-for-profit funding agencies.

Ethics statement: This study obtained ethics approval from the Ethical Review Committee of the University of Sargodha (No. SU/REC/1491).

Consent to participate: Not applicable.

Data availability: The data supporting this study's findings are available from the corresponding author, Nabeel Ahmed, upon reasonable request.

Acknowledgments: The authors acknowledge the support of Ms. Khushbu Khalid in developing the study's scoring system and Dr. Hafiz Rashid Hussain for facilitating data collection at the College of Pharmacy, University of Sargodha.

Conflicts of interest: The authors declare no conflicts of interest.

References

[1] Boniol M, Kunjumen T, Nair TS, Siyam A, Campbell J, Diallo K. The global health workforce stock and distribution in 2020 and 2030: a threat to equity and 'universal' health coverage? BMJ Glob Health. 2022;7(6):e009316. https://doi.org/10.1136/bmjgh-2022-009316

[2] Abdu-Aguye SN, Suleiman MM, Shehu A, Mohammed ENA. Factors influencing choice of a pharmacy degree and career preferences of final year pharmacy students in Northern Nigeria: a multi-institutional study. Niger J Pharm Res. 2022;18(2):125-34. https://doi.org/10.4314/njpr.v18i2.4

[3] Alhomoud FK, AlGhalawin L, AlGofari G, AlDjani W, Ameer A, Alhomoud F. Career choices and preferences of Saudi pharmacy undergraduates: a cross-sectional study. Saudi Pharm J. 2019;27(4):467-74. https://doi.org/10.1016/j.jsps.2019.01.009

[4] Gargalicano CAG, De Oca PR, Galicia H JrS, Arosa AAM, Radadon STA, Gargalicano FG. Factors that influence career choice of graduating pharmacy students. Int J Multidiscip Appl Bus Educ Res. 2023;4(2):663-70. https://doi.org/10.11594/ijmaber.04.02.32

[5] Malhi SM, Raza H, Ajmal K, Shamim S, Ata S, Farooq S, et al. Current status and future suggestions for improving the Pharm. D curriculum towards clinical pharmacy practice in Pakistan. Pharmacy. 2017;5(3):46. https://doi.org/10.3390/pharmacy5030046

[6] Pharmacy Council of Pakistan. Recognition status of pharmacy institutions. 2023 [cited 16 July 2024]. Available from: https://pcpisb.gov.pk/blog/index.htm.

[7] Ministry of National Health Services, Regulations & Coordination Islamabad. Pakistan: human resources for health vision (HRH) 2018 -30. 2024 [cited 16 July 2024]. Available from: https://nhsrc.gov.pk/SiteImage/Misc/files/HRH%20Vision%202018-30%20Final.pdf.

[8] Hirschi A, Koen J. Contemporary career orientations and career self-management: a review and integration. J Vocat Behav. 2021;126:103505. https://doi.org/10.1016/j.jvb.2020.103505

[9] Doden W, Grote G, Rigotti T. Does leader–member exchange buffer or intensify detrimental reactions to psychological contract breach? The role of employees' career orientation. J Vocat Behav. 2018;106:192-208. https://doi.org/10.1016/j.jvb.2018.02.004

[10] Goedereis EA, Mehta CM, Jones J, Ayotte BJ. "I want to focus on something that I feel really good about every day": career development in established adulthood. Acta Psychol. 2023;234:103863. https://doi.org/10.1016/j.actpsy.2023.103863

[11] Mutanga MB, Piyose PX, Ndovela SL. Factors affecting career preferences and pathways: insights from IT students. J Inf Syst Informatics. 2023;5(3):1111-22. https://doi.org/10.51519/journalisi.v5i3.556

[12] Al-Qudah RA, Abuhussein R, Hasen E, Rezeq M, Basheti IA. Factors influencing career choice among undergraduate pharmacy students at a private university in Jordan. Pharm Educ. 2019;19(1):56–61.

[13] Zhang T, Li L, Bian Y. Final-year pharmacy undergraduate students' career intention and its influencing factors: a questionnaire study in northwest China. BMC Med Educ. 2020;20:405. https://doi.org/10.1186/s12909-020-02342-8

[14] Arbab AH, Eltahir YAM, Elsadig FS, Yousef BA. Career preference and factors influencing career choice among undergraduate pharmacy students at University of Khartoum, Sudan. Pharmacy. 2022;10(1):26. https://doi.org/10.3390/pharmacy10010026

[15] James PB, Pessima Batema MN, Bah AJ, Brewah TS, Kella AT, Lahai M, et al. Was pharmacy their preferred choice? Assessing pharmacy students' motivation to study pharmacy, attitudes, and future career intentions in Sierra Leone. Health Prof Educ. 2018;4(2):139–48. https://doi.org/10.1016/j.hpe.2017.06.001

[16] Mubarak N, Arif S, Irshad M, Aqeel RM, Khalid A, Ijaz UE, et al. How are we educating future physicians and pharmacists in Pakistan? A survey of the medical and pharmacy students' perception on learning and preparedness to assume future roles in antibiotic use and resistance. Antibiotics. 2021;10(10):1204. https://doi.org/10.3390/antibiotics10101204

[17] Khurshid F, Alharbi F, Almohydib A, Malik SI, Al-Omar HA, Alsultan MS, et al. Preparatory year students' perception of pharmacy profession as a career choice: a cross-sectional study. Braz J Pharm Sci. 2023;59:e21476. https://doi.org/10.1590/s2175-97902023e21476

[18] University of Sargodha. About us. 2024 [cited 16 July 2024]. Available from: https://su.edu.pk/aboutus.

[19] OpenEpi. Sample Size Calculator. 2024 [cited 16 July 2024]. Available from: https://www.openepi.com/SampleSize/SSPropor.htm.

[20] Saleem Z, Saeed H, Azhar F, Shafaqat I, Shahzadi S, Salman M, et al. Career preferences, leadership attitudes, and research interests among pharmacy students of Lahore, Pakistan. J Appl Pharm Sci. 2018;8(6):178–84. https://doi.org/10.7324/JAPS.2018.8624
[21] Mukattash TL, Nuseir KQ, Biltaji E, Jarab AS, Alefan Q. Students' perceptions of pharmacy as a specialization and their future career: a cross-sectional study of final-year pharmacy students in Jordan. Jordan J Pharm Sci. 2015;8(3):195–204.
[22] Gebremariam ET, Gadisa DA. Factors affecting the quality of undergraduate pharmacy students' research projects at Ambo University, Ethiopia: a qualitative study from advisors' perspective. Adv Med Educ Pract. 2021;12:745-54. https://doi.org/10.2147/AMEP.S316201
[23] Gebremariam ET, Gadisa DA. Evaluation of the undergraduate pharmacy student research projects in Ambo University, Ethiopia: retrospective review. Adv Med Educ Pract. 2021;12:205–13. https://doi.org/10.2147/AMEP.S297038
[24] Mukhalalati B, Elshami S, Adlan O, Elshazly M, Awaisu A, Stewart D, et al. Perceptions and experiences of undergraduate pharmacy students and alumni toward research after exposure to undergraduate research courses. Front Med. 2022;9:988908. https://doi.org/10.3389/fmed.2022.988908
[25] Adebisi YA. Undergraduate students' involvement in research: values, benefits, barriers and recommendations. Ann Med Surg. 2022;81:104384. https://doi.org/10.1016/j.amsu.2022.104384
[26] Cooper KM, Gin LE, Barnes ME, Brownell SE. An exploratory study of students with depression in undergraduate research experiences. CBE Life Sci Educ. 2020;19(2):ar19. https://doi.org/10.1187/cbe.19-11-0217
[27] Rahmah DDN, Putri AP. Improving student career maturity through peer group counseling. Int J Multicult Multireligious Underst. 2021;8(8):256-62. https://doi.org/10.18415/ijmmu.v8i8.2904
[28] Almalki OS, Alqarni TA, Alharthi RM, Algarni MA, Mohamed Ibrahim MI, Asiri YA, et al. Career readiness among Saudi pharmacy students: exploring the need for and the impact of career counseling services. Adv Med Educ Pract. 2022;13:1267–77. https://doi.org/10.2147/AMEP.S375929
[29] Ives RC, Klein KC, Mason NA. Career and professional development services for pharmacy students. Curr Pharm Teach Learn. 2020;12(9):1110–15. https://doi.org/10.1016/j.cptl.2020.04.026
[30] Hussain M, Sahudin S, Fauzi SM, Manaf NA, Wahab MSA. Exploring pharmacy students' chosen career path: a year-on-year perspective. High Educ. 2021;81:1257–72. https://doi.org/10.1007/s10734-020-00610-6
[31] Jarab AS, Al-Qerem W, Mukattash TL. Career choices of Pharmacy and Pharm D undergraduates: attitudes and preferences. Heliyon. 2021;7(3):e06448. https://doi.org/10.1016/j.heliyon.2021.e06448
[32] Pasha A, Siddiqui DA. Factors influencing professional selection choices: evidence from Pakistan. Eur J Bus Manag. 2019;11(36):137-53. https://doi.org/10.2139/ssrn.3641642
[33] Sajjad B, Ishaq R, Iqbal Q, Saleem F. A progressive assessment of pharmacy undergraduates' motivation and satisfaction towards pharmacy as a professional choice. J Pharm Pract Community Med. 2021;7(1):14–18. https://doi.org/10.5530/jppcm.2021.1.3
[34] Koçak O, Ak N, Erdem SS, Sinan M, Younis MZ, Erdoğan A. The role of family influence and academic satisfaction on career decision-making self-efficacy and happiness. Int J Environ Res Public Health. 2021;18(11):5919. https://doi.org/10.3390/ijerph18115919
[35] Alrasheedy AA, Ibrahim MH, Alsahali S, Alfadly SO, Siddeeg K, Salah GB, et al. Current state of career placement and employment opportunities for Doctor of Pharmacy graduates: a cross-sectional analysis from a college of pharmacy, Saudi Arabia. Saudi Pharm J. 2022;30(10):1479–85. https://doi.org/10.1016/j.jsps.2022.07.010
[36] Almarzoky Abuhussain SS, Elrggal ME, Salamatullah AK, Althobaity AA, Alotaibi AF, Almeleebia TM, et al. Work readiness scale for pharmacy interns and graduates: a cross-sectional study. Saudi Pharm J. 2021;29(9):976–80. https://doi.org/10.1016/j.jsps.2021.07.018
[37] Wong WJ, Lee RFS, Chong LY, Lee SWH, Lau WM. Work readiness of pharmacy graduates: an exploratory study. Explor Res Clin Soc Pharm. 2024;13:100389. https://doi.org/10.1016/j.rcsop.2023.100389
[38] Malau-Aduli BS, Jones K, Alele F, Adu MD, Drovandi A, Knott G, Young L, Jo C. Readiness to enter the workforce: perceptions of health professions students at a regional Australian university. BMC Med Educ. 2022;22:89. https://doi.org/10.1186/s12909-022-03120-4
[39] Sartika D, Nengsi AR. Work readiness of graduates responding to user needs for a "Ready to Work" workforce from university perspective. Idarah J Pendidik Dan Kependidik. 2022;6(1):37–50.
[40] Kinnane P, Kennedy N, Quinton A. Work readiness attributes: comparative views of clinical supervisors and final year sonography students. Sonography. 2021;8(3):82–9. https://doi.org/10.1002/sono.12274
[41] Thabit AK, Alghamdi DI, Alaqi RO, Alsufyani MA, Bagalagel AA,. Factors influencing future career interests of pharmacy interns in Saudi Arabia: a survey from 25 colleges of pharmacy. BMC Med Educ. 2023;23:35. https://doi.org/10.1186/s12909-023-04022-9
[42] Almaghaslah D, Alsayari A, Almanasef M, Asiri A. A cross-sectional study on pharmacy students' career choices in the light of Saudi Vision 2030: will community pharmacy continue to be the most promising, but least preferred, sector? Int J Environ Res Public Health. 2021;18(9):4589. https://doi.org/10.3390/ijerph18094589
[43] Othman MI, Mohd Najib MN, Sulaiman S, Abdul Khalid MI, Zamri MI, Mohd Shakri MS, et al. Pathway to success: exploring students' perspectives on career aspirations in pharmacy. Jurnal Intelek. 2024;19(1):103–14.

[44] Fitzpatrick KL, Allen EA, Griffin BT, O'Shea JP, Dalton K, Bennett-Lenane H. Exploring career choices of pharmacy graduates over 15 years: a cross-sectional evaluation. Curr Pharm Teach Learn. 2024;16(5):307–18. https://doi.org/10.1016/j.cptl.2024.02.010

[45] DeRemer CE, Shaddock R, Anderson KV, Curtis SD. Measuring the immediate impact when first year pharmacy students are introduced to diverse career pathways. Curr Pharm Teach Learn. 2021;13(11):1503–9. https://doi.org/10.1016/j.cptl.2021.09.008

[46] Younes S, Halat DH, Rahal M, Hendaus M, Mourad N. Motivation, satisfaction, and future career intentions of pharmacy students: a cross-sectional preliminary analysis. Curr Pharm Teach Learn. 2022;14(11):1365–72. https://doi.org/10.1016/j.cptl.2022.09.026

[47] Alnahar SA, Mamiya KT, John C, Bader L, Bates I. Experience with pharmacy academic programmes and career aspirations of pharmacy students and young pharmacists—an international cross-sectional study. BMC Med Educ. 2022;22:444. https://doi.org/10.1186/s12909-022-03510-8

Bulletin of
Pharmaceutical & Medicinal Research

Original Article

Standard treatment guidelines and clinical decision-making in type 2 diabetes mellitus: insights from tertiary care healthcare providers in Islamabad

Awais Ejaz [a,*], Sibgha Usman [b], Nargis Javaid [c]

[a] Al Ehsan Hospital, Mareer Chowke, Murree Road, Rawalpindi
[b] University of Health Sciences, Pakistan
[c] Central Institute of Family Medicine, Pakistan

* Correspondence: rph.awais@gmail.com

Citation: Ejaz A, Usman S, Javaid N. Standard treatment guidelines and clinical decision-making in type 2 diabetes mellitus: insights from tertiary care healthcare providers in Islamabad. Bull Pharm Med Res. 2024;3:49-57.

Received: 29 July 2024
Revised: 17 October 2024
Accepted: 04 November 2024
Published: 31 December 2024

Publisher's Note: Logixs Journals remains neutral concerning jurisdictional claims in its published subject matter, including maps and institutional affiliations.

Abstract

Diabetes mellitus (DM) is an illness caused by either a relative or absolute loss of insulin; it is highly prevalent worldwide. The role of standard treatment guidelines (STGs) is fundamental to ensure positive treatment outcomes for type 2 diabetes mellitus (T2DM), as they promote rationality in prescriptions. This descriptive cross-sectional study aimed to determine healthcare providers' perceptions of STGs for T2DM management, perceived barriers to T2DM management, and perceptions of the effectiveness of oral antidiabetics. Furthermore, the study also examined the associations of knowledge with the dose of antidiabetic agent, sector of employment and clinical experience. This study included 150 healthcare providers working in public and private tertiary care facilities in Islamabad. A relevant expert-verified questionnaire was employed in the study, and data were gathered via a convenient sampling technique. The results of the study revealed that 38.67% of the providers were from the public sector and that 61.33% of the providers were from the private sector. A total of 87.33% of the providers agreed that current antidiabetic drugs are effective, and 77.33% supported combination therapy; 64.00% reported that STGs are cost effective, and 94.67% underlined the importance of educational program treatment outcomes; 88.67% of the providers highlighted patient-related barriers, 80.67% highlighted limited guideline availability, and 80.00% highlighted a lack of prescriber awareness as major barriers in the implementation of STGs. Glimepiride by 82.00% of providers and metformin by 73.33% of providers were rated as most effective, whereas glibenclamide was the least preferred agent by 61.33% of providers. The level of knowledge varied, with sector showing a significant association (p = 0.001), whereas experience had no significant impact (p = 0.503). The study concluded that healthcare providers support the effectiveness of oral antidiabetics and the use of combination therapy, and the role of treatment guidelines in T2DM management, patient-related barriers, limited access to STGs, and discrepancies in knowledge across sectors remain major challenges in T2DM management.

Keywords

Type II diabetes mellitus; Standard treatment guidelines; Rational prescribing; Pharmacy practice; Healthcare provider perceptions; Prescribing practices

1. Introduction

Diabetes mellitus (DM) is a complex metabolic disorder that is characterized by either a relative or absolute deficiency of insulin secretion by the pancreas in the human body [1]. The clinical features of this disease include impaired glucose tolerance and dysregulation of lipid and protein metabolism [2]. The global incidence of type 2 diabetes mellitus (T2DM) has been assessed over the past two decades through the DiaMond Pro-

ject, which provides comprehensive data on newly diagnosed and existing cases from both developed and developing countries and maintains registries of patients diagnosed with T2DM [3]. Approximately 24 such registries are operational in the USA; the estimated prevalence of diabetes in the USA was 35 million in 2000, with a projected increase to approximately 64 million by the year 2025. Moreover, 52% of these cohorts are residents of the Caribbean and Latin America, where the prevalence of diabetes is expected to increase to 62% by the year 2025, accounting for 40 million individuals with T2DM [4,5]. In Australia, the prevalence of diabetes is recorded to be 7.4%, with an additional 16.4% of the population classified as diabetic; this figure has increased twofold since 1981, a tendency that cannot be attributed solely to demographic shifts or rising obesity rates [6].

The prevalence of diabetes in developing nations is a significant public health challenge, with females being affected by T2DM compared with their male counterparts; 32% of Asian Indians in Tanzania and 28% of urban male Micronesians in Kiribati have T2DM. Age-specific analyses revealed a consistent, directly proportional trend toward an increase in T2DM incidence with increasing age. In developing countries, there is a considerable burden of T2DM; 20% to even 50% of cases remain undiagnosed and are not reported at any healthcare facility [7]. Specifically, in Pakistan, the incidence of T2DM is increasing, and the World Health Organization (WHO) indicated that 11.77% of the population is affected by this condition, with males accounting for 11.20% and females accounting for 9.19% of the reported cases [8]. These statistical figures highlight T2DM as a growing public health disaster in developing countries, demanding the urgent attention of healthcare providers and interventions in both clinical and community settings [9].

Adherence to standard treatment guidelines (STGs) is important to ensure that healthcare providers appropriately prescribe medicines by considering the dose, frequency, route of administration, bioavailability and overall clinical effectiveness of the drug to improve the clinical condition and symptoms of patients [9]. Various factors contribute to variations in prescribing trends and practices by healthcare providers for patients with similar clinical features, requiring adherence to STGs for appropriate clinical outcomes [10]. These guidelines are usually developed by health organizations or regulatory bodies on a national or regional basis, and it is legally binding upon the government of the land to implement them uniformly across the country to maintain consistency in treatment protocols.

In the management of T2DM, multiple factors, such as prescribing patterns, treatment costs, and adherence to guidelines by prescribers, play important roles in optimizing clinical care and treatment outcomes [11]. Adherence to treatment includes both the patient's commitment to follow prescribed regimens and the physician's compliance with healthcare regulations and standardized clinical protocols [12,13]. Improved adherence not only enhances glycemic control but also reduces the risk of diabetes-related complications in most patients with T2DM [14]. Therefore, improving both provider and patient compliance with STGs is key to the successful management of T2DM worldwide.

Understanding the perceptions of healthcare providers of oral antidiabetics, particularly their clinical effectiveness and efficacy when used in combination therapy, is important for evaluating prescribing practice trends for the management of T2DM [15]. Similarly, assessment of the perceived clinical effectiveness and implementation of STGs and understanding of patient-related barriers and institutional limitations helps in the identification of loopholes in the system and draws attention to collaborative actions with intersectoral approaches to address these issues [16]. Furthermore, knowledge among healthcare providers regarding appropriate doses of antidiabetics is essential for safe and effective management of T2DM. This study was conducted to assess the perceptions of healthcare providers on STGs for T2DM management, perceived barriers in T2DM man-

agement, and perceptions of the effectiveness of oral antidiabetics. Furthermore, the study also examined the associations of knowledge with the dose of antidiabetic agent, sector of employment and clinical experience.

2. Materials and methods

2.1. Study design

This descriptive cross-sectional study was conducted over a period of three months, from January to March 2024.

2.2. Ethical approval

Ethical approval for the study was obtained from the Ethical Review Committee of Hamdard University, Islamabad (No. HU/ERC/2024/269).

2.3. Study setting

The study was conducted in Islamabad, the capital city of Pakistan, which comprises an urban area of 220.15 square kilometers and a rural area of 466.20 square kilometers. The city has a population of 2,003,368 and a literacy rate of 88% [17,18]. The city has several public and private tertiary healthcare facilities, many of which provide specialized diabetes care services.

2.4. Study population

The study targeted healthcare providers (medical officers and consultants) working at public and private tertiary healthcare facilities in Islamabad.

2.5. Inclusion and exclusion criteria

The study included all healthcare providers, including physicians and consultants, who held a valid medical license, were employed at public or private tertiary healthcare facilities, and were directly involved in clinical decision-making and patient care, with a minimum of two years of relevant working experience. However, healthcare providers who did not provide written informed consent were excluded from the study.

2.6. Sample size and sampling technique

The sample size for this descriptive cross-sectional study was calculated via the OpenEpi sample size calculator, assuming a 95% confidence level (Z = 1.96), a 5% margin of error (d), and an estimated prevalence of 6.00% on the basis of a prior study in Pakistan reporting that only a small proportion of physicians followed the diabetic guidelines [19,20]. The minimum sample size required was calculated to be 87, but it was increased to 174 to account for nonresponders and to strengthen the validity of the findings of the study. A convenient sampling technique was used to target healthcare providers at tertiary-level healthcare facilities.

2.7. Study instrument

A semistructured questionnaire was developed on the basis of the WHO guidelines for the standard care and clinical practice of T2DM [21]. It was assessed by field experts for content validity and pilot tested on 10 respondents whose data were not included in the final analysis.

2.8. Study measures

The questionnaire collected sociodemographic information of the healthcare providers, including type of hospital (public or private) and years of clinical experience. The second section of the questionnaire captured the responses of healthcare providers regarding T2DM management via a 3-point Likert scale (disagree, neutral, agree) across four major domains: perceived effectiveness of currently available antidiabetic medications, appropriateness of combination therapy in clinical practice, perceived impact of STGs on cost-effectiveness, and the role of educational programs in improving T2DM management. The third section of the questionnaire collected information on barriers perceived by healthcare providers for the management of T2DM by using the same 3-point Likert scale across five areas, including patient-related factors (noncompliance, socioeconomic constraints, and literacy levels), the availability of STGs, a lack of prescriber awareness, the clinical experience of healthcare providers in decision-making, and a lack of STG enforcement at healthcare facilities. The fourth section of the questionnaire assessed healthcare providers' perceptions of the clinical effectiveness of oral antidiabetics as monotherapies and combination regimens. The respondents had to rate each effectiveness of each drug on a 3-point Likert scale (least effective, neutral, most effective). The final section of the questionnaire evaluated the knowledge of healthcare providers regarding the appropriate dosing of commonly used oral antidiabetics. This section of the questionnaire included multiple-choice and true/false items evaluating key areas of clinical practice, such as initial and maintenance dosing, the maximum recommended dose, adjustment of the dose in patients with renal impairment, and contraindicated drugs. Each correct response was given one point, whereas incorrect or unanswered items received zero points, resulting in a total possible score ranging from 0-10 for the section.

2.9. Data collection procedure

The initial phase of the data collection consisted of training the data collection team by the relevant experts, followed by training, and the data collection team was then sent to the targeted healthcare facilities. Prior permission for data collection was obtained from the concerned authorities of the targeted healthcare facilities. Informed written consent was obtained from the healthcare providers eligible for the study who were willing to participate in the study, and the study objectives were clearly explained to the respondents. Data were collected via face–to-face interviews with healthcare providers with the help of the developed semistructured questionnaire.

2.10. Data analysis

The data were analyzed via IBM SPSS Statistics version 25. Descriptive statistics, including frequencies and percentages, were used to summarize categorical variables. The chi-square test was applied to assess the associations between knowledge of oral antidiabetic drug dosing and healthcare provider characteristics, including sectors of employment (public or private) and years of clinical experience. A p value of less than 0.05 was considered statistically significant.

3. Results

Among the 174 healthcare providers, 150 completed face-to-face interviews, for a participation rate of 86.21%. Among them, 38.67% (n = 58) were from public hospitals, and 61.33% (n = 92) were from private hospitals. In terms of clinical experience, 9.33% (n

= 14) had less than one year, 32.00% (n = 48) had 1 to 5 years, 27.33% (n = 41) had 6 to 10 years, and 31.33% (n = 47) had more than 10 years of experience.

Table 1 shows that 87.33% (n = 131) of healthcare providers agreed on the effectiveness of the current antidiabetic drugs available in hospitals, whereas 12.67% (n = 19) disagreed. Regarding the appropriateness of combination therapy, 77.33% (n = 116) agreed, and 22.67% (n = 34) disagreed. For the impact of STGs on cost-effectiveness, 64.00% (n = 96) agreed, and 36.00% disagreed. A large majority, 94.67% (n = 142), agreed that educational programs play a role in improving T2DM management, with only 5.33% (n = 8) disagreeing.

Table 1. Perceptions of T2DM treatment and STGs.

Variable	Disagree	Neutral	Agree
	Frequency (%)	Frequency (%)	Frequency (%)
Perceived effectiveness of current drugs in hospitals	19 (12.67)	0 (0.00)	131 (87.33)
Appropriateness of combination therapy in clinical practice	34 (22.67)	0 (0.00)	116 (77.33)
Standard Treatment Guidelines' impact on cost-effectiveness	54 (36.00)	0 (0.00)	96 (64.00)
Role of educational programs in improving T2DM management	8 (5.33)	0 (0.00)	142 (94.67)

Table 2 shows that 88.67% (n = 133) of healthcare providers agreed that patient-related factors are a barrier in T2DM management, whereas 11.33% (n = 17) disagreed. With respect to the availability of guidelines, 80.67% agreed that it was a barrier, and 19.33% (n = 29) disagreed. Similarly, 80.00% (n = 121) identified a lack of prescriber awareness as a barrier, with 20.00% (n = 30) disagreeing. Most respondents (94.67%, n = 142) agreed that the prescriber's clinical experience plays a critical role in T2DM management, and 5.33% (n = 8) disagreed. Additionally, 80.67% (n = 121) considered a lack of guideline enforcement a barrier, whereas 19.33% (n = 29) disagreed.

Table 2. Perceived barriers in T2DM management.

Variable	Disagree	Neutral	Agree
	Frequency (%)	Frequency (%)	Frequency (%)
Patient related factors	17 (11.33)	0 (0.00)	133 (88.67)
Availability of guidelines	29 (19.33)	0 (0.00)	121 (80.67)
Lack of prescriber awareness	30 (20.00)	0 (0.00)	120 (80.00)
Prescriber's clinical experience	8 (5.33)	0 (0.00)	142 (94.67)
Lack of guidelines enforcement	29 (19.33)	0 (0.00)	121 (80.67)

Table 3 indicates that glimepiride was viewed as the most effective monotherapy by 82.00% of the respondents (n = 123). This was followed closely by metformin and gliclazide, both of which were rated as effective by 73.33% of the respondents (n = 110 each), and pioglitazone, which was rated as effective by 72.00% (n = 108). In terms of combination therapies, respondents showed a stronger preference for combination therapies than for monotherapies, as evidenced by the higher percentage of providers rating these combinations as the most effective. Metformin combined with glimepiride was considered the most effective drug by 80.00% of the providers (n = 120). This was followed by metformin with gliclazide, which was rated effective by 74.00% of the respondents (n = 111), and metformin with pioglitazone, which was rated effective by 70.67% (n = 106). Glibenclamide was rated as the least effective, with only 61.33% of respondents (n = 92) considering it effective and only 38.67% (n = 58) rating it as the most effective.

Table 3. Perceived effectiveness of oral antidiabetic drugs (OADs).

Variable	Least Effective	Neutral	Most Effective
	Frequency (%)	Frequency (%)	Frequency (%)
Metformin	40 (26.67)	0 (0.00)	110 (73.33)
Pioglitazone	42 (28.00)	0 (0.00)	108 (72.00)
Gliclazide	40 (26.67)	0 (0.00)	110 (73.33)
Glimepiride	27 (18.00)	0 (0.00)	123 (82.00)
Metformin + Glimepiride	30 (20.00)	0 (0.00)	120 (80.00)
Metformin + Pioglitazone	44 (29.33)	0 (0.00)	106 (70.67)
Metformin + Gliclazide	39 (26.00)	0 (0.00)	111 (74.00)
Glibenclamide	92 (61.33)	0 (0.00)	58 (38.67)

Table 4 shows a statistically significant association between healthcare providers' sector of employment and their knowledge of oral antidiabetic drug dosing ($p = 0.001$). Among the public sector respondents, 34.48% had poor knowledge, 48.28% had moderate knowledge, and 17.24% had good knowledge. In contrast, in the private sector, 20.65% had poor knowledge, 43.48% had moderate knowledge, and 35.87% had good knowledge. No statistically significant association was found between years of clinical experience and knowledge level ($p = 0.503$).

Table 4. Associations between knowledge of oral antidiabetic dose, sector, and experience.

Variables	N	Knowledge Level			Degree of Freedom (df)	*p* Value
		Poor (0–3) (N = 39)	Moderate (4–6) (N = 68)	Good (7–10) (N = 43)		
		Frequency (%)	Frequency (%)	Frequency (%)		
Public sector	58	20 (34.48)	28 (48.28)	10 (17.24)	2	0.001 *
Private sector	92	19 (20.65)	40 (43.48)	33 (35.87)		
< 1 year	14	5 (35.71)	7 (50.00)	2 (14.29)	3	0.503
1 – 5 years	48	13 (27.08)	24 (50.00)	11 (22.98)		
6 – 10 years	41	9 (21.95)	17 (41.46)	15 (36.59)		
> 10 years	47	12 (25.53)	20 (42.55)	15 (31.91)		

* Data were analyzed via chi-square test. ** Significant value ($p < 0.05$).

4. Discussion

The findings of the present study indicate that a significant proportion of healthcare providers perceive the currently available oral antidiabetic medications in tertiary care hospitals as effective for managing T2DM. Furthermore, most providers advocate for the use of combination therapy; however, some dissent shows varying clinical perspectives. STGs are generally regarded as beneficial for enhancing the clinical effectiveness of antidiabetic therapy; however, their impact is not completely acknowledged by healthcare providers. Continuous medical education is considered important by most healthcare providers to improve T2DM management. Healthcare providers have identified several barriers to the effective management of T2DM, including patient-related factors such as nonadherence to therapy, financial constraints, and low health literacy. The clinical experience of healthcare providers is widely recognized as an important factor in clinical decision-making, but understanding the appropriate dose of antidiabetics varies across different healthcare sectors, with limited correlation with years of experience and the clinical practice of healthcare providers.

A study conducted in the United Kingdom (UK) revealed that, despite the absence of STGs in healthcare facilities, over 85% of general practitioners reported having access to

and regularly using the National Institute for Health and Care Excellence (NICE) guidelines for the clinical management of diabetes [22,23]. Similarly, an Australian study highlighted better compliance with national diabetes care guidelines; furthermore, the guidelines were uniformly implemented across the country through electronic medical systems and were a part of the continuous professional education of healthcare providers [24].

The results of our study regarding clinical effectiveness with respect to adherence to STGs contradict those of a study from Thailand, which revealed that STG implementation significantly reduced direct medical costs while maintaining good glycemic control among T2DM patients [25]. Moreover, healthcare providers recognized the importance of training programs to improve T2DM management in line with a multicenter Indian study, which revealed that frequent continuing medical education (CME) sessions increased healthcare providers' adherence to the Indian Council of Medical Research (ICMR) guidelines for the management of T2DM [26].

The current study identified metformin and glimepiride as the most effective drugs regarded by healthcare providers, which aligns with prescribing practices in the United States (US), where metformin continues to be recognized as the first-line treatment according to the American Diabetes Association (ADA), whereas glimepiride is typically utilized as a second-line agent. Furthermore, in Canada and South Africa, glibenclamide has been withdrawn from the market and is not recommended for diabetes management because of its associated risk of hypoglycemia in patients with T2DM; these findings are in line with those of the current study in which glibenclamide was least preferred by healthcare providers [27,28]. However, the preference of healthcare providers for combination therapy is consistent with the international literature, and a study from Spain highlighted that compared with combination therapy, monotherapy had a better effect on glycemic control in patients with moderate-to-severe T2DM [29].

The results of the current study that indicate that STG compliance increases cost-effectiveness contrast with the findings of German and Swedish studies, which highlight that STGs both improve clinical outcomes and reduce unnecessary costs [30]. Furthermore, the current study revealed a statistically significant difference in the knowledge of healthcare providers between the public and private sectors, where private-sector healthcare providers showed higher levels of understanding of antidiabetic doses. This finding contrasts with that of a study in Ethiopia, which revealed that public sector healthcare providers had better knowledge of doses because of institutionalized training programs for effective STGs implementation [31].

The study was conducted in Islamabad, and a semistructured questionnaire was developed by using WHO guidelines, which is a valuable addition to the literature. Furthermore, the study highlighted the perceptions of healthcare providers regarding STGs and determined the associations among the public and private sectors as well as the experiences of healthcare providers. However, qualitative factors for prescribing trends and clinical practices were not taken into consideration, which remains a disadvantage of the study.

5. Conclusions

This study revealed that healthcare providers in tertiary care hospitals of Islamabad largely recognized the effectiveness of oral antidiabetic agents, particularly glimepiride, metformin, and gliclazide, with combination therapies such as metformin, glimepiride perceived as most effective for glycemic control in patients with T2DM. Most respondents acknowledged the importance of STGs for rational prescribing and cost-effectiveness; however, patient-related factors, limited guideline availability, lack of prescriber

awareness, and insufficient enforcement were identified as key barriers to their consistent use. Most healthcare providers agreed that educational programs contribute to improved T2DM management. The study also found a statistically significant association between healthcare sector and knowledge of oral antidiabetic dosing, with private-sector providers demonstrating comparatively higher knowledge levels, while clinical experience showed no significant association with dosing knowledge.

Author contributions: Conceptualization, AE, SU, and NJ; methodology, AE, SU, and NJ; software, AE, and SU; validation, AE, and SU; formal analysis, AE; investigation, AE, and SU; resources, AE, and NJ; data curation, AE and NJ; writing—original draft preparation, AE, SU, and NJ; writing—review and editing, AE, SU, and NJ; visualization, AE and SU; supervision, AE, and NJ; project administration, AE, and NJ. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no specific grant from the public, commercial, or not-for-profit funding agencies.

Ethics statement: Ethical approval for this study was obtained from the Ethical Review Committee of Hamdard University, Islamabad (No. HU/ERC/2024/269).

Consent to participate: Not Applicable.

Data availability: The data supporting this study's findings are available from the corresponding author, Awais Ejaz, upon reasonable request.

Acknowledgments: None.

Conflicts of interest: The authors declare no conflicts of interest.

References

[1] Mohajan D, Mohajan HK. Basic concepts of diabetics mellitus for the welfare of general patients. J Stud Soc Sci Humanit. 2023;
[2] 2(6):23–31. https://doi.org/10.56397/SSSH.2023.06.03
[3] Rauzier C, Chartrand DJ, Alméras N, Lemieux I, Larose E, Mathieu P, et al. Associations of insulin-like growth factor binding protein-2 with metabolic profile and hepatic fat deposition in asymptomatic men and women. Am J Physiol Endocrinol Metab. 2023;325(1):e99–105. https://doi.org/10.1152/ajpendo.00108.2023
[4] Hormazábal-Aguayo I, Ezzatvar Y, Huerta-Uribe N, Ramírez-Vélez R, Izquierdo M, García-Hermoso A. Incidence of type 1 diabetes mellitus in children and adolescents under 20 years of age across 55 countries from 2000 to 2022: a systematic review with meta-analysis. Diabetes Metab Res Rev. 2024;40(3):e3749. https://doi.org/10.1002/dmrr.3749
[5] Jensen ET, Dabelea DA, Praveen PA, Amutha A, Hockett CW, Isom SP, et al. Comparison of the incidence of diabetes in United States and Indian youth: an international harmonization of youth diabetes registries. Pediatr Diabetes. 2021;22:8–14. https://doi.org/10.1111/pedi.13009
[6] Zimbudzi E, Okada H, Funnell MM, Hamaguchi M. Editorial: innovation in diabetes self–care management and interventions. Front Endocrinol. 2023;14:1269437. https://doi.org/10.3389/fendo.2023.1269437
[7] Dunstan DW, Zimmet PZ, Welborn TA, De Courten MP, Cameron AJ, Sicree RA, et al. The rising prevalence of diabetes and impaired glucose tolerance: the Australian diabetes, obesity and lifestyle study. Diabetes Care. 2002;25(5):829–34. https://doi.org/10.2337/diacare.25.5.829
[8] Cheema A, Adeloye D, Sidhu S, Sridhar D, Chan KY. Urbanization and prevalence of type 2 diabetes in Southern Asia: a systematic analysis. J Glob Health. 2014;4(1):010404. https://doi.org/10.7189/jogh.04.010404
[9] Meo SA, Zia I, Bukhari IA, Arain SA. Type 2 diabetes mellitus in Pakistan: current prevalence and future forecast. J Pak Med Assoc. 2016;66(12):1637–42
[10] Pruette CS, Amaral S. Empowering patients to adhere to their treatment regimens: a multifaceted approach. Pediatr Transplant. 2021;25:e13849. https://doi.org/10.1111/petr.13849
[11] Govender T, Suleman F, Perumal-Pillay VA. Evaluating the implementation of the standard treatment guidelines (STGs) and essential medicines list (EML) at a public South African tertiary institution and its associated primary health care (PHC) facilities. J Pharm Policy Pract. 2021;14:105. https://doi.org/10.1186/s40545-021-00390-z
[12] Hannan A. Smallholder tea economy in Assam and North Bengal. The smallholder tea economy and regional development: perspectives from India. Cham: Springer International Publishing; 2024. p. 49–69.
[13] Świątoniowska-Lonc N, Tański W, Polański J, Jankowska-Polańska B, Mazur G. Psychosocial determinants of treatment adherence in patients with type 2 diabetes: a review. Diabetes Metab Syndr Obes. 2021;14:2701-15. https://doi.org/10.2147/dmso.s308322

[14] Wiedenmayer K, Ombaka E, Kabudi B, Canavan R, Rajkumar S, Chilunda F, et al. Adherence to standard treatment guidelines among prescribers in primary healthcare facilities in the Dodoma region of Tanzania. BMC Health Serv Res. 2021;21:272. https://doi.org/10.1186/s12913-021-06257-y
[15] Rhee MK, Slocum W, Ziemer DC, Culler SD, Cook CB, El-Kebbi IM, et al. Patient adherence improves glycemic control. Diabetes Educ. 2005;31(2):240–50. https://doi.org/10.1177/0145721705274927
[16] Dankoly US, Vissers D, El Farkouch Z, Kolasa E, Ziyyat A, Rompaey BV, et al. Perceived barriers, benefits, facilitators, and attitudes of health professionals towards multidisciplinary team care in type 2 diabetes management: a systematic review. Curr Diabetes Rev. 2021;17(6):e111020187812. https://doi.org/10.2174/1573399816999201110200126
[17] Kumar P, Sinha AK, Kumar A, Alam ME. Barriers and facilitators of providing standard of care diabetes management at primary care level in geriatric population. J Family Med Prim Care. 2022;11(10):6451–7. https://doi.org/10.4103/jfmpc.jfmpc_851_22
[18] Pakistan Bureau of Statistics. Home. 2024 [cited 21 April 2024]. Available from: https://www.pbs.gov.pk/sites/default/files/population/2017/results/13501.pdf.
[19] Islamabad Capital Territory Administration. Geography, climate & demographics. 2024 [cited 21 April 2024]. Available from: https://ictadministration.gov.pk/geography-climate-demographics/.
[20] OpenEPI. Open source statistics for public health. 2024 [cited 21 April 2024]. Available from: https://www.openepi.com/SampleSize/SSPropor.htm.
[21] Hashmi NR, Khan SA. Interventional study to improve diabetic guidelines adherence using mobile health (m-Health) technology in Lahore, Pakistan. BMJ Open. 2018;8(5):e020094. https://doi.org/10.1136/bmjopen-2017-020094
[22] World Health Organization. Management of diabetes mellitus: standards of care and clinical practice guidelines. 2024 [cited 21 April 2024]. Available from: https://applications.emro.who.int/dsaf/dsa509.pdf.
[23] Fisher M, Drummond R. Guidelines on antidiabetic drugs. In: Fisher M, McKay GA, Llano A, editors. Diabetes drug notes. New Jersey: Wiley-Blackwell; 2022. p. 294–321.
[24] Haque A. Few UK vascular centres offer a fully NICE-compliant supervised exercise programme: a national audit. Ann R Coll Surg Engl. 2022;104(2):130–7. https://doi.org/10.1308/rcsann.2021.0126
[25] Speight J, Skinner TC, Dunning T, Black T, Kilov G, Lee C, et al. Our language matters: improving communication with and about people with diabetes. A position statement by Diabetes Australia. Diabetes Res Clin Pract. 2021;173:108655. https://doi.org/10.1016/j.diabres.2021.108655
[26] Wongrith P, Thiraratanasunthon P, Kaewsawat S, Le CN. Comparison of self-management between glycemic controlled and uncontrolled type-2 diabetic elderly in Thailand: a qualitative study. Sakharnyy Diabet. 2022;25(2):174–85. https://doi.org/10.14341/dm12417
[27] Wander GS, Panda JK, Pal J, Mathur G, Sahay R, Tiwaskar M, et al. Management of hypertension in patients with type 2 diabetes mellitus: Indian guideline 2024 by Association of Physicians of India and Indian College of Physicians. J Assoc Physicians India. 2024;72(8):e1–25. https://doi.org/10.59556/japi.72.0620
[28] Kalra S, Das AK, Fariduddin M, Shaikh K, Shah P, Rehim AA, et al. Glucodynamics and glucocracy in type 2 diabetes mellitus: clinical evidence and practice-based opinion on modern sulfonylurea use, from an International Expert Group (South Asia, Middle East & Africa) via modified Delphi method. Curr Med Res Opin. 2021;37(3):403–9. https://doi.org/10.1080/03007995.2020.1864309
[29] Nguyen JV, Roseberry S, Rivas JA, Cauthon KAB. Hypoglycemia in older people with type 2 diabetes: prevention and treatment strategies for outpatient and long-term care facility settings. Sr Care Pharm. 2021;36(2):112–23. https://doi.org/10.4140/TCP.n.2021.112
[30] Jódar E, Romera I, Wang Q, Roche SL, García-Pérez LE. Glycaemic variability in patients with type 2 diabetes mellitus treated with dulaglutide, with and without concomitant insulin: post hoc analyses of randomized clinical trials. Diabetes Obes Metab. 2022;24(4):631–40. https://doi.org/10.1111/dom.14615
[31] Gotham D, Moja L, van der Heijden M, Paulin S, Smith I, Beyer P. Reimbursement models to tackle market failures for antimicrobials: approaches taken in France, Germany, Sweden, the United Kingdom, and the United States. Health Policy. 2021;125(3):296–306. https://doi.org/10.1016/j.healthpol.2020.11.015
[32] Tegegne M. Perception towards performance appraisal practice and associated factors among health professionals in Central Gondar Zone primary hospitals, Ethiopia, 2022 [dissertation]. Gondar (ET): University of Gondar; 2022.